Organic & Biomolecular Chemistry

PAPER

Cite this: *Org. Biomol. Chem.*, 2017, **15**, 2003

Diastereoselective synthesis of tetrahydropyrans *via* Prins–Ritter and Prins–arylthiolation cyclization reactions†

Nabajyoti Hazarika,[a,b] Barnali Sarmah,[a,b] Manobjyoti Bordoloi,[a] Prodeep Phukan*[b] and Gakul Baishya*[a]

Received 9th December 2016,
Accepted 1st February 2017

DOI: 10.1039/c6ob02692c

rsc.li/obc

An efficient method has been developed for the synthesis of two new classes of tetrahydropyran derivatives comprising amide, tetrazole or benzothiazole moieties *via* a three-component reaction of 6-methylhept-5-en-2-ol, arylaldehydes and nitriles/thiols in the presence of a tetrafluoroboric acid diethyl ether complex. The reaction proceeds *via* the formation of an oxocarbenium ion. This protocol is highly diastereoselective and only single diastereomer has been isolated in each case.

Introduction

Multi-component reactions (MCRs) are important synthetic methodologies which can easily give complex organic molecules from readily available starting materials in a single step chemical process. Atom economy is a major advantage of MCRs, because, the final product of most of the multi-component reactions contains all the atoms of the starting materials.[1] In addition, the continuous demand for environmentally benign and economically viable synthetic processes has been inspiring synthetic organic chemists to develop one-pot multi-component reactions. The MCRs that consist of different sequential or tandem chemical reactions efficiently allow the creation of structurally complex organic molecules by reducing the reaction steps.[2]

The tetrahydropyran unit is considered to be an important target because of its presence in a variety of biologically active natural products, marine toxins and pheromones.[3] The well-known Prins cyclization reaction has emerged as a powerful synthetic tool for obtaining this type of six-membered heterocyclic compound in a single step chemical process.[4] Some recent reports have drawn attention to the use of the oxocarbenium–ene cyclization technique for the synthesis of tetrahydropyran ring systems.[5,6] Moreover, an extensive study on this cyclization reaction has been made by Mikami *et al.*[5a] This protocol provides not only tetrahydropyran derivatives but also other cyclic ethers such as tetrahydrofurans and oxabicyclic compounds. Although the undeniable benefits of oxocarbenium–ene cyclization reactions are well established in the literature, the applicability of this technique could be further extended to synthesize versatile oxa-cycles of biological importance.

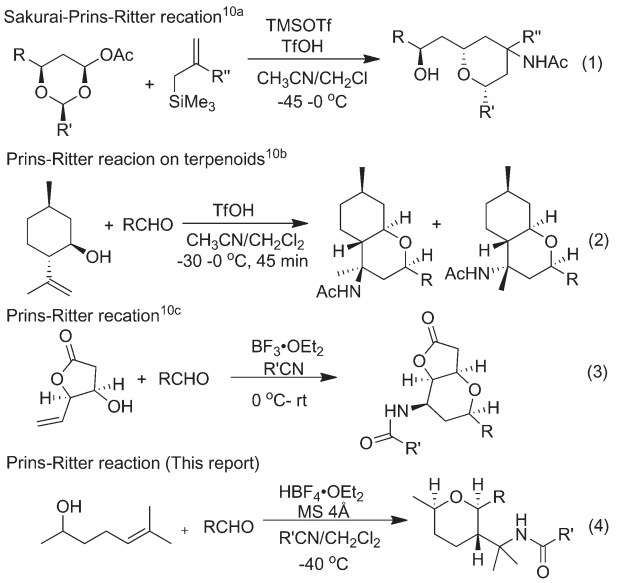
Again, the development of cost effective techniques for amide formation is a great challenge because of the importance of this linkage in chemistry and biology. The reaction of amines with carboxylic acids or with carboxylic acid derivatives such as acylhalides, anhydrides and esters in the presence of a coupling reagent and a tertiary amine is the widely used traditional method for the synthesis of amides.[7] The well-known Ritter reaction of nitriles has been used as an important synthetic methodology to obtain amides from carbocation precursors like alcohols and olefins in the presence of a strong acid.[8] A few modified Ritter reactions are known in the literature where *tert*-butylacetate is used as a source of carbocation.[9] The applicability of this reaction has been realized from different domino multi-component reactions where it acts as a terminator of a particular reaction sequence such as the Sakurai–Prins–Ritter reaction and the Prins–Ritter reaction (Scheme 1, eqn (1)–(3)).[10] These reports of domino Ritter reactions have focused on the synthesis of different libraries of 4-amido tetrahydropyran derivatives by using various Lewis acids and Brønsted acids as efficient acid promoters.[11] Recently, we have also reported two novel approaches of a one-pot Schmidt and Ritter reaction sequence to obtain large collections of amides which have been a part of different pharmaceutically important drug molecules.[12]

Herein, we report a novel method for the synthesis of a new class of tetrahydropyran derivatives bearing an amide

[a]*Chemical Science & Technology Division, CSIR-North East Institute of Science and Technology, Jorhat-785006, India. E-mail: b.gakul@gmail.com; Fax: +913762370011; Tel: +913762372948*

[b]*Department of Chemistry, Gauhati University, Guwahati-14, India*

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of all compounds, and NOESY spectrum of **7da**. CCDC 1502070. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ob02692c



Scheme 1 Domino Ritter reactions for the synthesis of versatile building blocks.

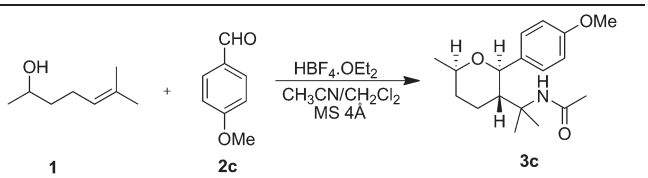
functionality by using the concept of the Prins–Ritter cyclization reaction sequence (Scheme 1, eqn (4)). This reaction is believed to proceed through the formation of an oxocarbenium ion in the presence of $HBF_4{\cdot}OEt_2$ that undergoes an intramolecular cyclization reaction to provide the tetrahydropyran ring.

Results and discussion

Recently, we disclosed a synthetic methodology for the synthesis of angularly fused pyranochromenes *via* the [4 + 2]-cycloaddition reaction of *o*-quinonemethides generated *in situ* from different salicylaldehydes and 6-methylhept-5-en-2-ol. In the same report we observed that *p*-anisaldehyde also underwent the cyclization reaction giving the tetrahydropyran derivative, but the mechanistic pathway by which the cyclization process ended is the oxocarbenium–ene reaction instead of the [4 + 2]-cycloaddition reaction.[13] Therefore, it could also be assumed that the reaction might proceed through a (3,5)-oxocarbenium–ene cyclization pathway where the cyclization occurred in a step-wise manner *via* the formation of a carbocation intermediate followed by an intra-molecular attack of this carbocation by the phenolic hydroxyl group adjacent to the aldehydic group to form the cyclized product.[14] Hence, we thought of trapping the carbocation by an external nucleophile such as a nitrile molecule in order to produce a new class of tetrahydropyran derivatives by this novel protocol of the Prins–Ritter cyclization reaction (Scheme 1, eqn (4)). Initially, we performed the reaction of 6-methylhept-5-en-2-ol (**1**) with *p*-anisaldehyde (**2c**) in a 1 : 1 mixture of CH_2Cl_2 and acetonitrile in the presence of 4 Å molecular sieves by using 1 equiv. of $HBF_4{\cdot}OEt_2$ as an acid promoter at room temperature. But the reaction resulted in a mixture of spots (as observed by TLC) instead of giving the desired Ritter product (Table 1, entry 1). Repetition of the same reaction at 0 °C and at −10 °C failed to eliminate the formation of by-products (Table 1, entries 2 & 3). Virtually, we considered performing the reaction at a lower temperature to reduce the formation of multiple products. Thus, we performed the same reaction at −20 °C by using 1 equiv. of $HBF_4{\cdot}OEt_2$. This time, the reaction proceeded smoothly affording the oxocarbenium-Ritter product **3c** as a single diastereomer (confirmed by its ^{1}H NMR spectrum) along with other unidentified products. After column chromatography purification we obtained a 39% yield of **3c** (Table 1, entry 4). In order to increase the yield of the product **3c**, we thought of performing the same reaction by using the acid-promoter in more than one equivalent and accordingly, we carried out the same reaction in three different sets where $HBF_4{\cdot}OEt_2$ was added in 1.5, 2.0 and 3.0 equivalents. Surprisingly, the above three experiments furnished the Prins–Ritter product **3c** in 51%, 54%, and 52% yields, respectively (Table 1, entries 5–7). However, 15–20% of the unidentified product was also formed in each case. To minimize the formation of by-products, the reaction was further performed at different low temperatures such as −25 °C, −40 °C and −50 °C (Table 1, entries 8–10); and among all, the reaction at −40 °C gave the product **3c** with the highest yield of 64%. From the above experiments, we concluded that the formation of the by-products cannot be completely shunned. Thus, the optimal reaction conditions involved the use of 6-methylhept-5-en-2-ol (**1**, 1.0 mmol), *p*-anisaldehyde (**2c**, 1.2 mmol) and $HBF_4{\cdot}OEt_2$ (2.0 mmol) in 2 mL of a 1 : 1 mixture of CH_2Cl_2 and acetonitrile at −40 °C (Table 1, entry 9).

Furthermore, the efficacy of the acid-promoter $HBF_4{\cdot}OEt_2$ was compared with other Lewis acids and Brønsted acids such as $BF_3{\cdot}OEt_2$, TfOH, CCl_3COOH and AcOH by performing the same reaction under the optimized reaction conditions

Table 1 Reaction optimization studies[a]



Entry	Catalyst (equiv.)	Temperature	Time (h)	Yields[b] (%)
1	$HBF_4{\cdot}OEt_2$(1.0)	25 °C	2	—
2	$HBF_4{\cdot}OEt_2$(1.0)	0 °C	2	—
3	$HBF_4{\cdot}OEt_2$(1.0)	−10 °C	2	—
4	$HBF_4{\cdot}OEt_2$(1.0)	−20 °C	2	39
5	$HBF_4{\cdot}OEt_2$(1.5)	−20 °C	2	51
6	$HBF_4{\cdot}OEt_2$(2.0)	−20 °C	2	54
7	$HBF_4{\cdot}OEt_2$(3.0)	−20 °C	2	52
8	$HBF_4{\cdot}OEt_2$(2.0)	−25 °C	2	51
9	$HBF_4{\cdot}OEt_2$(2.0)	−40 °C	2	64
10	$HBF_4{\cdot}OEt_2$(2.0)	−50 °C	2	61

[a] Reaction conditions: Reaction performed with **2c** (1.2 mmol) and **1** (1 mmol) and the ratio of CH_3CN/CH_2Cl_2 (1 : 1) in 2 mL solution in the presence of 100 mg 4 Å MS. [b] Yields are for the isolated products.

Table 2 Comparison of $HBF_4{\cdot}OEt_2$ with different acid promoters for the synthesis of **3c**[a]

Entry	Catalyst	Equivalent	Time (h)	Yield[b] (%)
1	$BF_3{\cdot}OEt_2$	1	2	36
2	$BF_3{\cdot}OEt_2$	2	2	60
3	TfOH	1	2	25
4	TfOH	2	2	50
5	CCl_3CO_2H	1	2	15
6	CCl_3CO_2H	2	2	31
7	AcOH	1	2	0
8	AcOH	2	2	0
9	AcOH	3	2	0
10	AcOH[c]	—	2	0

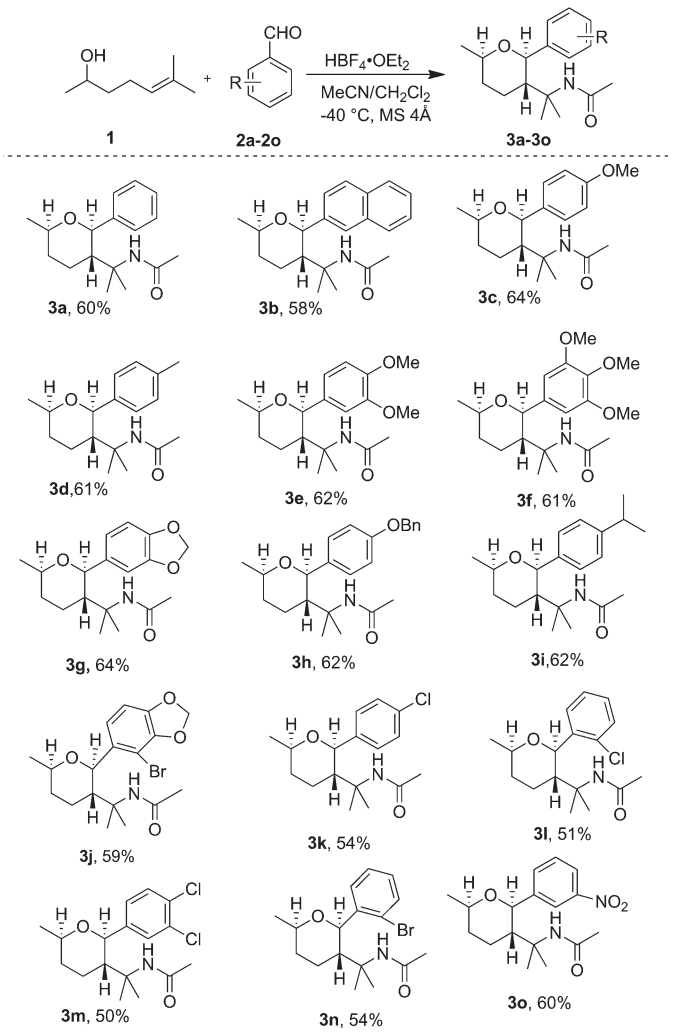
[a] Reaction conditions: Reaction performed with **2c** (1.2 mmol) and **1** (1 mmol) and ratio of CH_3CN/CH_2Cl_2 (1 : 1) in 2 mL solution in the presence of 100 mg 4 Å MS. [b] Yields refer to the isolated products. [c] Reaction performed in 1 : 1 mixture AcOH and acetonitrile (2 mL).

(Table 2, entries 1–10). Among all, two equiv. of $BF_3{\cdot}OEt_2$ gave the product **3c** in 60% yield (Table 2, entry 2). Similarly, two equiv. of each TfOH and CCl_3COOH also promoted the reaction, but the product was obtained in moderate yields (Table 2, entries 4 & 6). Neither a stoichiometric nor an excess amount of AcOH was effective for this transformation (Table 2, entries 7–10).

With the optimal reaction conditions in hand, we explored the general applicability and scope of this protocol with various aromatic and aliphatic aldehydes, and the results have been presented in Table 3. We started the protocol by performing the reaction of **1** with unsubstituted benzaldehyde (**2a**) and 2-naphthaldehyde (**2b**), and both smoothly underwent the Prins–Ritter cyclization reaction affording their corresponding tetrahydropyran derivatives **3a** and **3b** in 60% and 58% yields, respectively (Table 3). The optimization studies already proved that an aromatic aldehyde bearing an electron donating substituent *i.e.* *p*-anisaldehyde (**2c**) worked well in this reaction. Similarly, *p*-tolualdehyde (**2d**), 3,4-dimethoxybenzaldehyde (**2e**), 3,4,5-trimethoxybenzaldehyde (**2f**), piperonaldehyde (**2g**), *p*-benzyloxybenzaldehyde (**2h**) and *p*-isopropylbenzaldehyde (**2i**) also underwent the reaction affording their respective cyclized products **3d**, **3e**, **3f**, **3g**, **3h** and **3i** in good yields (Table 3). Arylaldehydes containing electron withdrawing groups also underwent the Prins–Ritter cyclization reaction, but their tetrahydropyran derivatives (**3k–3m**) were obtained in lower yields relative to those offered by electron donating substituents except for 3-nitrobenzaldehyde (**2o**) which gave 60% yield of the corresponding product **3o** (Table 3). Products were obtained as single diastereomers in all cases.

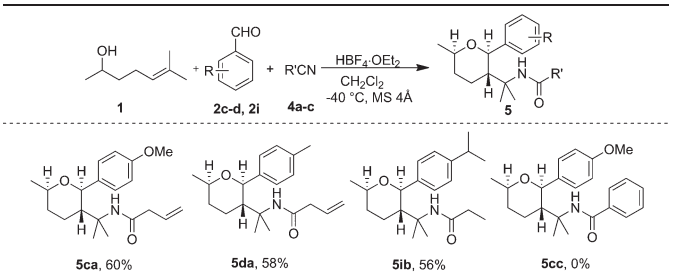
After successful utilization of acetonitrile as a Ritter counterpart of the reaction, we concentrated on the use of different nitrile molecules in order to complete the cyclization process. Accordingly, we chose allylnitrile (**4a**), propionitrile (**4b**) and benzonitrile (**4c**) as our Ritter reaction counterparts (Table 4). When the alkenol **1** was reacted with **2c** and **2d** in the presence of **4a** under the standard reaction conditions in two different experiments, their respective products **5ca** and **5da** were isolated in good yields. Similarly, propionitrile (**4b**) also participated well in this one-pot three-component reaction affording the respective cyclized product **5ib** in 56% yield.

Table 3 Scope of the Prins–Ritter cyclization reaction[a,b]



[a] Reaction conditions: Reaction performed with **2** (1.2 mmol) and **1** (1 mmol) and ratio of CH_3CN/CH_2Cl_2 (1 : 1) in 2 mL solution in the presence of 100 mg 4 Å MS. [b] Yields refer to the isolated products.

Table 4 Scope of nitriles[a,b]



[a] Reaction conditions: Reaction performed with **1** (1.0 mmol), **2** (1.2 mmol) and **4** (2.0 mmol) in CH_2Cl_2 (2 mL) in the presence of 100 mg 4 Å MS. [b] Yields refer to the isolated products.

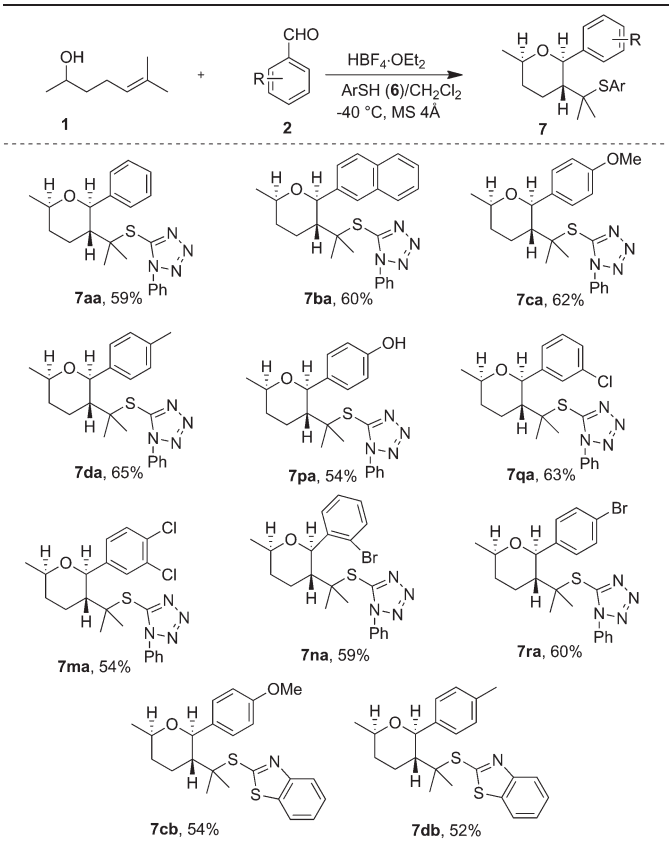
However, benzonitrile (**4c**) did not take part in the reaction (Table 4).

After successful application of the Prins–Ritter cyclization reaction on 6-methylhept-5-en-2-ol (**1**), we moved to explore another one-pot three-component reaction that is the Prins–arylthiolation cyclization reaction for the synthesis of tetrahydropyran derivatives containing 1-(methyl-ethylsulfanyl)-1-phenyl-1-*H*-tetrazole and 1-(methyl-ethylsulfanyl)benzothiazole moieties. Organic molecules bearing sulphur atoms have been commonly found in nature and they also play important roles in many biological structures and functions.[15] Recently, organic chemists have been attracted towards the synthesis of nitrogen containing heterocycles due to their versatile applications as pesticides, herbicides and also as cytotoxic agents. 2-Mercaptobenzothiazole derivatives are an important class of heterocyclic compounds which possess potential antibacterial and antifungal activities.[16] The benzothiazole moiety plays an important role in medicinal chemistry due to its wide range of biological activities including anti-tubercular, -inflammatory, -tumor, -amoebic, -parkinsonian, -thelmintic, -hypertensive, -hyperlipidemic, -ulcer, chemoprotective and selective CCR3 receptor antagonist activities.[16] Due to the presence of sulfur and nitrogen atoms, both 1-phenyl-1*H*-tetrazolethiol (**6a**) and 2-mercaptobenzothiazole (**6b**) exhibit excellent nucleophilic properties. Therefore, we also aim to terminate the cyclization process of the above mentioned cyclization reaction by thiol nucleophiles **6a** & **6b** instead of nitrile molecules. Accordingly, the reaction of **1** with **2c** was carried out in the presence of **6a** under the standard reaction conditions and the reaction smoothly took place affording the respective cyclized product **7ca** in 62% yield. The reaction was generalized by employing different aldehydes (**2a–d**, **2m–n** & **2p–r**) and both thiol nucleophiles **6a** and **6b**; and the results are summarized in Table 5. It was observed that arylaldehydes having both electron donating (**2c–d** & **2p**) and electron withdrawing groups (**2m–n**, **2q–r**) yielded the desired products in good yields. Both **6a** and **6b** worked well under these reaction conditions. Similarly, as obtained in the Prins–Ritter cyclization reaction, products **7** were also isolated as single diastereomers in all cases (Table 5).

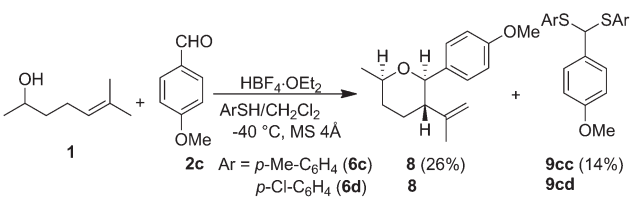
However, under the optimized reaction conditions the reactions of **1** and **2c** with *p*-methylthiophenol (**6c**) gave a complex reaction mixture and after careful separation we isolated the ene-product **8** in 26% yield and the dithioacetal **9cc** in 14% yield. Again, the reaction of **1** and **2c** with *p*-chlorothiophenol (**6d**) produced an inseparable mixture of **8** & **9cd** (Scheme 2).

A possible mechanism for these two transformations has been proposed in Scheme 3. The reaction proceeds with the protonation of the aldehyde group by $HBF_4{\cdot}OEt_2$ at the initial stage which facilitates the attack of the hydroxyl group present in the 6-methylhept-5-en-2-ol molecule. The subsequent proton transfer followed by the removal of a water molecule leads to the oxocarbenium ion **A**. The oxocarbenium ion **A** after intramolecular cyclization gives the carbocation **B**. Then, the nucleophile present in the reaction media (either nitrile or thiol) attacks the carbocation **B**. In the case of nitrile, it gives

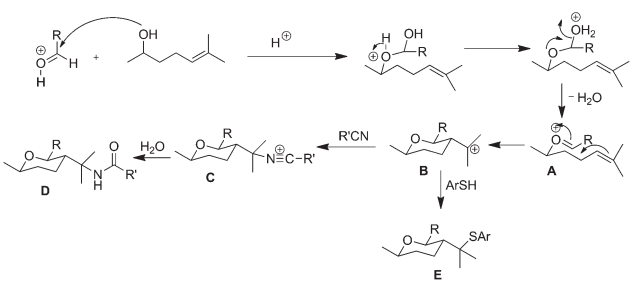
Table 5 Scope of the Prins–arylthiolation cyclization reaction[a,b]



[a] Reaction conditions: Reaction performed with **2** (1.2 mmol), **1** (1 mmol) and **6** (1.2 mmol) in CH_2Cl_2 (2 mL) solution in the presence of 100 mg 4 Å MS. [b] Yields refer to the isolated products.



Scheme 2 Prins–arylthiolation cyclization reaction with other thiophenols.



Scheme 3 Mechanism of Prins–Ritter and Prins–arylthiolation cyclization reactions.

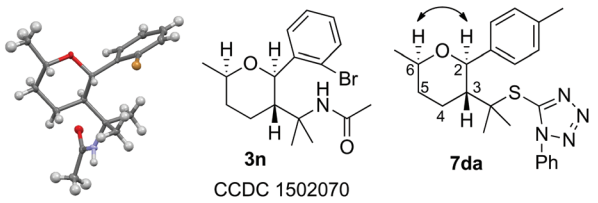


Fig. 1 Single X-ray crystallographic structure of compound **3n** and NOE diagram of compound **7da**.

the intermediate **C** which under hydrolysis gives the desired product **D**, whereas the attack by the thiol directly gives the product **E**. In all experiments only a single diastereomer was obtained which confirms the possibility of the formation of the carbocation **B** (chair conformer).

The structure of the products was established by the single X-ray crystallography[17] of the product **3n** (Fig. 1), which confirms the formation of the carbocation **B** in its stable 'chair conformer'. The structure of the products was also confirmed by the NOESY spectrum (see the ESI†) of compound **7da**, for which a strong NOE peak between the protons H-2 and H-6 and no NOE peak between H-2 and H-3 were observed which clearly established the proposed structure of **7** (Fig. 1).

Conclusions

In conclusion, an efficient method for the synthesis of versatile amide and thiol substituted tetrahydropyrans has been developed. A wide range of aromatic aldehydes with both electron donating and electron withdrawing substituents underwent Prins–Ritter and Prins–arylthiolation cyclization reactions with 6-methylhept-5-en-2-ol to give the tetrahydropyran derivatives in excellent diastereoselectivities and good yields. The applications of this reaction are under investigation in our laboratory.

Experimental section

General experimental details

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 500 and (125) MHz NMR spectrometers, respectively, using TMS as the internal standard. Mass spectra were recorded on a mass spectrometer. All the commercially available regents were used without further purification. All experiments were monitored by thin layer chromatography using aluminium pre-coated silica gel TLC plates. After elution, the plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved by staining anisaldehyde charring solution. Column chromatography was performed on silica gel (100–200 mesh) using an appropriate ethyl acetate–hexane mixture for elution.

General procedure for the preparation of compound 3. To a solution of 6-methylhept-5-en-2-ol (**1**, 1.0 mmol) and aldehyde **2** (1.2 mmol) in dry acetonitrile (1 mL) and dry CH_2Cl_2 (1 mL) was added 100 mg of activated 4 Å molecular sieves. To the same reaction mixture was added a solution of $HBF_4{\cdot}OEt_2$ (2.0 mmol in 0.5 mL CH_2Cl_2) dropwise (by syringe) at −40 °C and the mixture was stirred for 1 hour at the same temperature. Then the reaction mixture was allowed to warm up to room temperature over 1 hour. After completion of the reaction (as monitored by TLC) saturated aq. $NaHCO_3$ (10 mL) solution was added to the reaction mixture and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (1 × 10 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated using a rotary evaporator and column chromatographed on silica gel (100–200 mesh) using a 3 : 7 ethyl acetate–hexane mixture as the eluent to get the Prins–Ritter products **3**. 1.2 mmol of the nitrile compounds (**4a–4c**) was taken instead of acetonitrile for the synthesis of compounds **5**.

*N-(2-((2R,3S,6R)-6-Methyl-2-phenyltetrahydro-2H-pyran-3-yl) propan-2-yl)acetamide (**3a**).* White solid; mp 144–145 °C; IR ($CHCl_3$): 3432.9, 3311.2, 3029.5, 2972.3, 2930.5, 2860.3, 1655.2 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.29 (m, 3H), 7.25 (d, J = 7.0 Hz, 2H), 4.36 (s, 1H), 4.27 (d, J = 10.0 Hz, 1H), 3.52–3.47 (m, 1H), 2.52 (m, 1H), 2.03–2.00 (m, 1H), 1.76–1.73 (m, 1H), 1.52–1.41 (m, 2H), 1.34 (s, 3H), 1.22 (s, 6H), 1.20 (d, J = 10.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.96, 143.16, 128.77, 127.78, 127.50, 82.97, 73.93, 55.09, 45.70, 33.63, 26.53, 25.87, 24.03, 22.92, 21.92; MS (EI) m/z = 275 $[M]^+$, 276 $[M + H]^+$; Anal. Calcd for $C_{17}H_{25}NO_2$ C, 74.14; H, 9.15; N, 5.09. Found C, 74.28; H, 9.27; N, 4.91.

*N-(2-((2R,3S,6R)-6-Methyl-2-(naphthalen-2-yl)tetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3b**).* Brown solid; mp 141 °C; IR ($CHCl_3$): 3315.3, 2969.8, 2929.2, 1654.7 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85–7.78 (m, 3H), 7.57 (dd, J = 1.5 Hz, 8.5 Hz, 1H), 7.48–7.43 (m, 3H), 4.43 (d, J = 10.5 Hz, 1H), 4.24 (s, 1H), 3.55 (m, 1H), 2.68 (m, 1H), 2.05–1.79 (m, 1H), 1.77–1.63 (m, 1H), 1.55–1.44 (m, 2H), 1.35 (s, 3H), 1.24 (s, 3H), 1.23 (d, J = 6.0 Hz, 3H), 0.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.87, 140.42, 133.28, 133.02, 128.54, 127.75, 127.47, 126.26, 126.09, 125.91, 125.46, 83.19, 74.06, 55.12, 45.27, 33.67, 26.60, 25.98, 23.76, 23.13, 21.92; MS (EI) m/z = 325 $[M]^+$, 326 $[M + H]^+$; Anal. Calcd for $C_{21}H_{27}NO_2$ C, 77.50; H, 8.36; N, 4.30. Found C, 77.57; H, 8.44; N, 4.19.

*N-(2-((2R,3S,6R)-2-(4-Methoxyphenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3c**).* White solid; mp 103–104 °C; IR ($CHCl_3$): 3311.3, 2970.2, 2930.4, 1654.8 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 4.45 (s, 1H), 4.21 (d, J = 10.0 Hz, 1H), 3.82 (s, 3H), 3.74–3.47 (m, 1H), 2.45 (m, 1H), 2.08–1.98 (m, 2H), 1.75–1.68 (m, 1H), 1.50–1.37 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.22 (s, 3H), 1.19 (d, J = 13.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.02, 159.03, 135.37, 128.55, 114.15, 82.33, 73.93, 55.26, 55.24, 45.76, 40.67, 33.63, 26.44, 25.86, 24.13, 22.94, 21.92; MS (EI) m/z = 305 $[M]^+$, 306 $[M + H]^+$; Anal. Calcd for $C_{18}H_{27}NO_3$ C, 70.79; H, 8.91; N, 4.59. Found C, 70.68; H, 8.99; N, 4.51.

*N-(2-((2R,3S,6R)-6-Methyl-2-(p-tolyl)tetrahydro-2H-pyran-3-yl) propan-2-yl)acetamide (**3d**).* White solid; mp 127 °C; IR ($CHCl_3$): 3430.2, 2970.5, 2928.0, 1656.9, 1650.1 cm^{-1}; ^{1}H NMR

(500 MHz, $CDCl_3$): δ 7.30 (d, J = 6.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.44 (s, 1H), 4.26 (d, J = 10.5 Hz, 1H), 3.50 (m, 1H), 2.44 (m, 1H), 2.30 (s, 3H), 2.04–1.91 (m, 1H), 1.74–1.59 (m, 1H), 1.59–1.50 (m, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 1.26 (d, J = 10.0 Hz, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.89, 140.14, 137.38, 129.37, 127.37, 82.66, 73.90, 55.17, 45.95, 33.64, 26.46, 25.84, 23.92, 22.79, 22.35, 21.92, 20.96; ESI-HRMS (m/z) $[M + H]^+$ calcd for $C_{18}H_{28}NO_2$ 290.2120, found 290.2127.

*N-(2-((2R,3S,6R)-2-(3,4-Dimethoxyphenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3e**).* Slightly brownish solid; mp 159 °C; IR ($CHCl_3$): 3419.4, 3369.4, 2970.6, 2931.9, 2844.9, 1657.1, 1518.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (s, 1H), 6.95–6.78 (m, 2H), 4.44 (s, 1H), 4.21 (d, J = 9.5 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.51–3.47 (m, 1H), 2.59 (td, J = 3.5 Hz, 12.0 Hz, 1H), 2.04–1.98 (m, 1H), 1.75–1.71 (m, 1H), 1.53–1.40 (m, 2H), 1.38 (s, 3H), 1.30 (s, 3H), 1.18 (d, J = 2.5 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.93, 149.30, 148.54, 135.78, 120.06, 119.54, 110.86, 110.25, 82.77, 73.98, 55.92, 55.72, 55.08, 44.97, 33.59, 26.54, 25.94, 24.08, 23.97, 23.06, 21.90; ESI-HRMS (m/z) $[M + H]^+$ calcd for $C_{19}H_{30}NO_4$ 336.2175, found 336.2182.

*N-(2-((2R,3S,6R)-6-Methyl-2-(3,4,5-trimethoxyphenyl)tetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3f**).* White solid; mp 116 °C; IR ($CHCl_3$): 3323.8, 2969.8, 2930.4, 2843.5, 1654.8, 1593.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.56 (s, 2H), 4.49 (s, 1H), 4.14 (d, J = 10.0 Hz, 1H), 3.89 (s, 6H), 3.75 (s, 3H), 3.52–3.47 (m, 1H), 2.65 (m, 1H), 2.04–2.00 (m, 1H), 1.99–1.41 (m, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.20 (d, J = 6.5 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.04, 153.26, 138.54, 137.19, 104.43, 83.37, 74.13, 60.44, 56.04, 54.99, 44.63, 33.53, 26.67, 25.95, 24.10, 23.02, 21.90; MS (EI) m/z = 365 $[M]^+$, 366 $[M + H]^+$; Anal. Calcd for $C_{20}H_{31}NO_5$ C, 65.73; H, 8.55; N, 3.83. Found C, 65.81; H, 8.69; N, 3.70.

*N-(2-((2R,3S,6R)-2-(Benzo[d][1,3]dioxol-5-yl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3g**).* Brown solid; mp 136–138 °C; IR ($CHCl_3$): 3419.8, 3316.3, 3077.3, 2966.8, 2927.5, 2856.3, 1655.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H), 6.90–6.76 (m, 2H), 5.92 (dd, J = 1.0 Hz, 7.5 Hz, 2H), 4.50 (s, 1H), 4.17 (d, J = 10.0 Hz, 1H), 3.49 (m, 1H), 2.47–2.42 (m, 1H), 2.00–1.97 (m, 1H), 1.74–1.65 (m, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 1.22 (d, J = 2.5 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.77, 147.89, 147.03, 137.17, 120.78, 108.12, 108.00, 100.91, 82.69, 73.97, 55.15, 45.48, 33.58, 26.51, 25.87, 24.03, 23.09, 21.91; MS (EI) m/z = 319 $[M]^+$, 320 $[M + H]^+$; Anal. Calcd for $C_{18}H_{25}NO_4$ C, 67.69; H, 7.89; N, 4.39. Found C, 67.81; H, 7.99; N, 4.30.

*N-(2-((2R,3S,6R)-2-(4-(benzyloxy)phenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3h**).* White solid; mp 122–123 °C; IR ($CHCl_3$): 3425.4, 2970.9, 2929.1, 2860.7, 1654.2, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44–7.25 (m, 7H), 6.94 (d, J = 8.5 Hz, 2H), 5.05 (s, 2H), 4.39 (s, 1H), 4.20 (d, J = 10.0 Hz, 1H), 3.49 (m, 1H), 2.45 (m, 1H), 2.01–1.98 (m, 1H), 1.74–1.71 (m, 2H), 1.48–1.43 (m, 1H), 1.33 (s, 3H), 1.21 (s, 3H), 1.18 (d, J = 7.5 Hz, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.83, 158.14, 136.88, 135.68, 128.56, 128.48, 127.85, 127.14, 115.19, 82.35, 73.93, 69.83, 55.15, 45.76, 33.66, 26.48, 25.89, 24.14, 22.95, 21.93; MS (EI) m/z = 381 $[M]^+$, 382 $[M + H]^+$; Anal. Calcd for $C_{24}H_{31}NO_3$ C, 75.56; H, 8.19; N, 3.67. Found C, 75.49; H, 8.28; N, 3.55.

*N-(2-((2R,3S,6R)-2-(4-isopropylphenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3i**).* White solid; mp 111–112 °C; IR ($CHCl_3$): 3428.7, 3315.5, 3082.4, 2967.6, 2930.8, 2869.3, 1658.7 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.27 (m, 2H), 7.20 (d, J = 7.5 Hz, 2H), 4.43 (s, 1H), 4.23 (d, J = 10.0 Hz, 1H), 3.50–3.48 (m, 1H), 2.88–2.85 (m, 1H), 2.42 (t, J = 1.5 Hz, 1H), 2.02–1.99 (m, 1H), 1.75–1.72 (m, 1H), 1.48–1.40 (m, 2H), 1.34 (s, 3H), 1.25–1.12 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.89, 148.24, 140.56, 127.34, 126.88, 82.65, 73.88, 55.14, 53.33, 45.94, 33.81, 33.63, 30.79, 26.49, 26.27, 25.80, 24.03, 23.85, 23.78, 22.60, 21.92; MS (EI) m/z = 317 $[M]^+$, 318 $[M + H]^+$; Anal. Calcd for $C_{20}H_{31}NO_2$ C, 75.67; H, 9.84; N, 4.41. Found C, 75.60; H, 9.91; N, 4.32.

*N-(2-((2R,3S,6R)-2-(4-Bromobenzo[d][1,3]dioxol-5-yl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3j**).* White solid; mp 189–190 °C; IR ($CHCl_3$): 3307.6, 2971.5, 2930.0, 1654.7 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04–6.91 (m, 2H), 5.99–5.87 (m, 2H), 4.66–4.70 (m, 2H), 3.51–3.47 (m, 1H), 2.70 (m, 1H), 2.02–1.91 (m, 1H), 1.76–1.66 (m, 2H), 1.49–141 (m, 4H), 1.37 (s, 3H), 1.21 (s, 3H), 1.11 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.84, 147.78, 147.63, 135.58, 112.89, 112.00, 109.77, 101.68, 80.38, 74.04, 55.19, 44.32, 33.50, 26.81, 26.01, 24.75, 23.96, 21.87, 18.34; MS (EI) m/z = 397 $[M]^+$, 398 $[M + H]^+$; Anal. Calcd for $C_{18}H_{24}BrNO_4$ C, 54.28; H, 6.07; N, 3.52. Found C, 54.57; H, 6.23; N, 3.40.

*N-(2-((2R,3S,6R)-2-(4-Chlorophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3k**).* White solid; mp 98–100 °C; IR ($CHCl_3$): 3436.7, 3300.6, 2965.5, 2928.7, 2850.5, 1652.8, 1552.0 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (s, 4H), 4.41 (s, 1H), 4.22 (d, J = 10.5 Hz, 1H), 3.51 (m, 1H), 2.62 (td, J = 3.5 Hz, 12.0 Hz, 1H), 2.01–1.97 (m, 1H), 1.75–1.72 (m, 1H), 1.51–1.40 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.81, 141.72, 133.24, 128.91, 128.64, 82.22, 73.99, 55.03, 45.07, 33.53, 26.56, 25.91, 23.91, 23.50, 21.84; MS (EI) m/z = 309 $[M]^+$, 310 $[M + H]^+$; Anal. Calcd for $C_{17}H_{24}ClNO_2$ C, 65.90; H, 7.81; N, 4.52. Found C, 66.18; H, 7.89; N, 4.41.

*N-(2-((2R,3S,6R)-2-(2-Chlorophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3l**).* Slightly brownish solid; mp 174–175 °C; IR ($CHCl_3$): 3308.3, 3071.3, 2972.8, 2930.7, 1654.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61–7.51 (m, 1H), 7.37–7.22 (m, 2H), 7.20–7.12 (m, 1H), 4.81 (d, J = 9.5 Hz, 1H), 4.65 (s, 1H), 3.52–3.47 (m, 1H), 2.77 (m, 1H), 2.05–1.97 (m, 1H), 1.76–1.68 (m, 1H), 1.51–1.41 (m, 2H), 1.39 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H), 1.10 (d, J = 0.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.04, 140.69, 131.70, 130.18, 129.23, 128.54, 127.38, 77.36, 73.98, 55.09, 44.39, 33.50, 26.79, 26.03, 24.17, 23.92, 21.85; MS (EI) m/z = 309 $[M]^+$, 310 $[M + H]^+$; Anal. Calcd for $C_{17}H_{24}ClNO_2$ C, 65.90; H, 7.81; N, 4.52. Found C, 66.02; H, 7.89; N, 4.31.

*N-(2-((2R,3S,6R)-2-(3,4-Dichlorophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3m**).* White solid; mp 153 °C;

IR ($CHCl_3$): 3439.3, 3305.8, 3077.9, 2974.1, 2932.2, 2862.2, 1652.7, 1555.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.47–7.38 (m, 2H), 7.26–7.21 (m, 1H), 4.40 (s, 1H), 4.20–4.16 (m, 1H), 3.48–3.45 (m, 1H), 2.69–2.65 (m, 1H), 2.02–1.98 (m, 1H), 1.77–1.48 (m, 1H), 1.48–1.28 (m, 8H), 1.19 (d, J = 1.5 Hz, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.71, 143.37, 132.46, 131.45, 130.33, 129.62, 126.99, 81.89, 74.13, 54.96, 44.57, 33.42, 26.63, 25.91, 23.82, 21.79; MS (EI) m/z = 343 $[M]^+$, 344 $[M + H]^+$; Anal. Calcd for $C_{17}H_{23}Cl_2NO_2$ C, 59.31; H, 6.73; N, 4.07. Found C, 59.48; H, 6.83; N, 3.90.

*N-(2-((2R,3S,6R)-2-(2-Bromophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3n**).* White solid; mp 179–181 °C; IR ($CHCl_3$): 3306.2, 3068.5, 2973.2, 2931.0, 2846.2, 1655.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.56–7.47 (m, 2H), 7.38–7.30 (m, 1H), 7.11–7.05 (m, 1H), 4.76 (d, J = 10.0 Hz, 1H), 4.65 (s, 1H), 3.53–3.47 (m, 1H), 2.76 (s, 1H), 2.06–2.00 (m, 1H), 1.76–1.71 (m, 1H), 1.50–1.45 (m, 2H), 1.44 (s, 3H), 1.20–1.14 (m, 6H), 1.11 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.04, 142.28, 132.57, 130.48, 128.92, 127.95, 122.59, 80.22, 74.02, 55.15, 44.40, 33.50, 26.87, 26.02, 24.54, 23.97, 21.85; MS (EI) m/z = 353 $[M]^+$, 354 $[M + H]^+$; Anal. Calcd for $C_{17}H_{24}BrNO_2$ C, 57.63; H, 6.83; N, 3.95. Found C, 57.51; H, 6.96; N, 3.74.

*N-(2-((2R,3S,6R)-6-Methyl-2-(3-nitrophenyl)tetrahydro-2H-pyran-3-yl)propan-2-yl)acetamide (**3o**).* White solid; mp 153–154 °C; IR ($CHCl_3$): 3405.6, 3307.4, 3078.0, 2974.2, 2932.5, 2863.9, 1655.7, 1530.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.58 (m, 1H), 4.82 (s, 1H), 4.41–4.39 (d, J = 7.0 Hz, 1H), 3.55 (m, 1H), 2.87 (m, 1H), 2.05 (m, 1H), 1.77 (d, J = 12.5 Hz, 1H), 1.54–1.44 (m, 2H), 1.37 (s, 3H), 1.29 (s, 3H), 1.22–1.12 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.97, 147.85, 145.24, 133.99, 129.43, 122.56, 122.41, 82.13, 74.13, 54.97, 44.28, 33.39, 26.55, 25.86, 24.09, 23.67, 21.74; MS (EI) m/z = 320 $[M]^+$, 321 $[M + H]^+$; Anal. Calcd for $C_{17}H_{24}N_2O_4$ C, 63.73; H, 7.55; N, 8.74. Found C, 63.84; H, 7.63; N, 8.60.

*N-(2-((2R,3S,6R)-2-(4-Methoxyphenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)but-3-enamide (**5ca**).* Brown solid; mp 103–105 °C; IR ($CHCl_3$): 3419.5, 3319.6, 2965.5, 2929.3, 2844.8, 1655.7, 1514.7 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.27 (m, 2H), 6.88–6.87 (d, J = 7.5 Hz, 2H), 5.50 (m, 1H), 5.02 (d, J = 10.5 Hz, 1H), 4.91–4.91 (d, J = 1.5 Hz, 1H), 4.89 (d, J = 14.5 Hz, 1H), 4.87 (s, 1H), 4.19 (d, J = 10.0 Hz, 1H), 3.57 (s, 3H), 3.47 (m, 1H), 2.52 (m, 1H), 2.33–2.04 (m, 2H), 2.02–1.99 (m, 2H), 1.47–1.42 (m, 1H), 1.25 (s, 6H), 1.13 (d, J = 9.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.16, 159.03, 135.43, 131.49, 128.60, 118.64, 114.09, 113.77, 82.39, 73.91, 55.21, 45.41, 42.08, 33.66, 26.49, 25.98, 23.17, 21.91; MS (EI) m/z = 331 $[M]^+$, 332 $[M + H]^+$; Anal. Calcd for $C_{20}H_{29}NO_3$ C, 72.47; H, 8.82; N, 4.23. Found C, 72.35; H, 8.93; N, 3.99.

*N-(2-((2R,3S,6R)-6-Methyl-2-(p-tolyl)tetrahydro-2H-pyran-3-yl)propan-2-yl)but-3-enamide (**5da**).* White solid; mp 106–108 °C; IR ($CHCl_3$): 3324.6, 2965.5, 2928.1, 1654.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30–7.14 (m, 4H), 5.50–5.45 (m, 1H), 5.01 (d, J = 1.0 Hz, 1H), 4.85 (d, J = 17.0 Hz, 1H), 4.49 (s, 1H), 4.20 (d, J = 10.0 Hz, 1H), 3.49–3.46 (m, 1H), 2.53–2.49 (m, 1H), 2.25 (s, 3H), 2.20–2.15 (m, 2H), 2.02–1.99 (m, 1H), 1.74–1.64 (m, 3H), 1.38 (s, 3H), 1.29–1.11 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.13, 140.23, 137.31, 131.59, 129.35, 127.44, 118.50, 82.72, 73.90, 55.17, 45.45, 41.95, 33.65, 26.55, 25.95, 23.00, 21.92, 20.99; MS (EI) m/z = 315 $[M]^+$, 316 $[M + H]^+$; Anal. Calcd for $C_{20}H_{29}NO_2$ C, 76.15; H, 9.27; N, 4.44. Found C, 76.22; H, 9.33; N, 4.36.

*N-(2-((2R,3S,6R)-2-(4-Isopropylphenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)propionamide (**5ib**).* White solid; mp 87–90 °C; IR ($CHCl_3$): 3326.8, 2965.9, 2930.8, 2871.8, 1650.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, J = 7.0 Hz, 2H), 7.20 (d, J = 7.0 Hz, 2H), 4.39 (s, 1H), 4.24 (d, J = 9.0 Hz, 1H), 3.50–3.46 (m, 1H), 2.89–2.84 (m, 1H), 2.44–2.39 (m, 1H), 2.03 (t, J = 6.5 Hz, 1H), 1.74–1.47 (m, 1H), 1.45–1.34 (m, 6H), 1.33–1.16 (m, 13H), 0.78 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.19, 148.21, 140.67, 127.34, 126.80, 82.65, 73.85, 54.94, 46.10, 33.81, 33.67, 29.56, 26.57, 25.83, 23.89, 23.84, 23.72, 22.69, 21.94, 9.04, 9.01; MS (EI) m/z = 331 $[M]^+$, 332 $[M + H]^+$; Anal. Calcd for $C_{21}H_{33}NO_2$ C, 76.09; H, 10.03; N, 4.23. Found C, 76.32; H, 10.13; N, 4.09.

General procedure for the preparation of compound 7. To a solution of 6-methylhept-5-en-2-ol (**1**, 1.0 mmol), aldehyde **2** (1.2 mmol) and thiol **6** (1.1 mmol) in dry CH_2Cl_2 (2 mL) was added 100 mg of activated 4 Å molecular sieves. To the same reaction mixture was added a solution of $HBF_4{\cdot}OEt_2$ (2.0 mmol in 0.5 mL CH_2Cl_2) dropwise (by syringe) at −40 °C and the mixture was stirred for 1 hour at the same temperature. Then the reaction mixture was allowed to warm up to room temperature over 1 hour. After completion of the reaction (as monitored by TLC) saturated aq. $NaHCO_3$ (10 mL) solution was added to the reaction mixture and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (1 × 10 mL) and dried over anhydrous sodium sulfate. The organic layer was concentrated using a rotary evaporator and column chromatographed on silica gel (100–200 mesh) using 0.5: 9.5 ethyl acetate–hexane as the eluent to get the Prins-thiolated products **7**.

*5-((2-((2R,3R,6R)-6-Methyl-2-phenyltetrahydro-2H-pyran-3-yl)propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7aa**).* White solid; mp 107 °C; IR ($CHCl_3$): 3583.9, 3063.7, 3031.6, 2969.8, 2930.2, 2859.1, 1596.3, 1498.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.53–7.16 (m, 10H), 4.30 (d, J = 9.5 Hz, 1H), 3.52–3.48 (m, 1H), 2.75–2.70 (m, 1H), 2.28 (td, J = 3.5 Hz, 13 Hz, 1H), 1.78–1.75 (m, 1H), 1.62–1.48 (m, 2H), 1.38 (s, 3H), 1.23 (s, 3H), 1.19 (d, J = 4.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.59, 142.24, 133.66, 129.85, 129.33, 128.27, 128.07, 128.02, 124.47, 83.26, 73.96, 57.77, 47.40, 33.76, 27.65, 27.20, 26.91, 21.82; MS (EI) m/z = 394 $[M]^+$, 395 $[M + H]^+$; Anal. Calcd for $C_{22}H_{26}N_4OS$ C, 66.98; H, 6.64; N, 14.20. Found C, 67.15; H, 6.76; N, 13.98.

*5-((2-((2R,3R,6R)-6-Methyl-2-(naphthalen-2-yl)tetrahydro-2H-pyran-3-yl)propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7ba**).* White solid; mp 112–114 °C; IR ($CHCl_3$): 3057.6, 2971.1, 2931.8, 2862.9, 1952.1, 1597.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.73–7.72 (m, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.53–7.24 (m, 6H), 7.03 (d, J = 7.5 Hz, 2H), 4.48 (d, J = 9.5 Hz, 1H), 3.57–3.54 (m, 1H), 3.02–2.97 (m, 1H), 2.31–2.28 (m, 1H), 1.82–1.78 (m, 1H), 1.65–1.48 (m, 2H), 1.42 (s, 3H), 1.28 (s, 3H), 1.19 (d, J = 6.0 Hz,

3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.82, 139.85, 133.37, 133.32, 133.14, 129.70, 129.22, 127.95, 127.91, 127.51, 127.04, 126.05, 125.86, 125.81, 124.20, 83.34, 74.01, 57.17, 46.59, 33.78, 27.38, 27.00, 26.82, 26.72, 21.86; MS (EI) m/z = 444 $[M]^+$, 445 $[M + H]^+$; Anal. Calcd for $C_{26}H_{28}N_4OS$ C, 70.24; H, 6.35; N, 12.60. Found C, 70.45; H, 6.62; N, 12.41.

*5-((2-((2R,3R,6R)-2-(4-Methoxyphenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7ca**).* White solid; mp 110 °C; IR ($CHCl_3$): 2967.6, 2929.7, 1611.9, 1514.4 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.51 (m, 3H), 7.39–7.36 (m, 2H), 7.21–7.19 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 4.27 (d, J = 10.0 Hz, 1H), 3.72 (s, 3H), 3.51–3.47 (m, 1H), 2.70–2.65 (m, 1H), 2.26–2.04 (m, 1H), 1.77–1.74 (m, 1H), 1.62–1.51 (m, 2H), 1.43 (s, 3H), 1.22 (s, 3H), 1.17 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.37, 152.69, 134.59, 133.66, 129.84, 129.33, 129.11, 124.45, 113.61, 82.61, 73.90, 57.78, 55.07, 47.40, 33.77, 27.47, 27.13, 27.00, 21.83; MS (EI) m/z = 424 $[M]^+$, 425 $[M + H]^+$; Anal. Calcd for $C_{23}H_{28}N_4O_2S$ C, 65.07; H, 6.65; N, 13.20. Found C, 65.15; H, 6.74; N, 13.11.

*5-((2-((2R,3R,6R)-6-Methyl-2-(p-tolyl)tetrahydro-2H-pyran-3-yl) propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7da**).* White solid; mp 137 °C; IR ($CHCl_3$): 3583.8, 2969.7, 2929.2, 2858.2, 1596.5, 1515.4, 1498.3 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.50 (m, 3H), 7.40–7.36 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 4.25 (d, J = 9.5 Hz, 1H), 3.51–3.46 (m, 1H), 2.76–2.71 (m, 1H), 2.17 (s, 3H), 1.77–1.74 (m, 1H), 1.58 (s, 3H), 1.40 (s, 3H), 1.19 (s, 3H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.67, 139.34, 137.69, 133.71, 129.79, 129.32, 128.92, 127.91, 124.37, 83.04, 73.92, 57.77, 47.10, 33.78, 27.57, 27.18, 27.02, 21.83, 21.08; MS (EI) m/z = 408 $[M]^+$, 409 $[M + H]^+$; Anal. Calcd for $C_{23}H_{28}N_4OS$ C, 67.62; H, 6.91; N, 13.71. Found C, 67.75; H, 7.02; N, 13.59.

*4-((2R,3R,6R)-6-Methyl-3-(2-((1-phenyl-1H-tetrazol-5-yl)thio) propan-2-yl)tetrahydro-2H-pyran-2-yl)phenol (**7pa**).* White solid; mp 148–149 °C; IR ($CHCl_3$): 3336.7, 3068.6, 3017.4, 2971.6, 2932.3, 2865.5, 1615.0, 1596.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.49 (m, 3H), 7.40–7.36 (m, 2H), 7.08 (d, J = 6.0 Hz, 2H), 6.95 (s, broad, 1H), 6.60 (d, J = 8.0 Hz, 2H), 4.25 (d, J = 9.5 Hz, 1H), 3.53–3.47 (m, 1H), 2.63–2.58 (m, 1H), 2.28–2.21 (m, 1H), 1.75–1.73 (m, 1H), 1.66–1.42 (m, 2H), 1.33 (s, 3H), 1.26 (s, 3H), 1.25 (d, J = 5.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.25, 152.82, 133.45, 133.42, 130.08, 129.47, 129.22, 124.60, 115.40, 82.81, 74.10, 58.02, 47.51, 33.70, 27.68, 27.06, 27.00, 21.69; MS (EI) m/z = 410 $[M]^+$, 411 $[M + H]^+$; Anal. Calcd for $C_{22}H_{26}N_4O_2S$ C, 64.37; H, 6.38; N, 13.65. Found C, 64.45; H, 6.50; N, 13.52.

*5-((2-((2R,3R,6R)-2-(3-Chlorophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7qa**).* White solid; mp 121–123 °C; IR ($CHCl_3$): 3583.6, 3066.1, 2971.5, 2932.0, 2865.7, 1951.8, 1597.8, 1576.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54–7.51 (m, 3H), 7.38–7.36 (m, 2H), 7.31 (d, J = 2.0 Hz, 1H), 7.19–7.10 (m, 3H), 4.28 (d, J = 10.0 Hz, 1H), 3.51–3.48 (m, 1H), 2.78–2.73 (m, 1H), 2.27–2.24 (m, 1H), 1.79–1.75 (m, 1H), 1.60–1.50 (m, 2H), 1.44 (s, 3H), 1.30 (s, 3H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.51, 144.26, 134.04, 133.58, 129.90, 129.47, 129.44, 129.42, 129.39, 128.30, 128.13, 126.31, 124.35, 82.51, 74.03, 57.09, 47.21, 33.58, 27.42, 26.97, 26.86, 21.75; MS (EI) m/z = 428 $[M]^+$, 429 $[M + H]^+$; Anal. Calcd for $C_{22}H_{25}ClN_4OS$ C, 61.60; H, 5.87; N, 13.06. Found C, 61.85; H, 5.94; N, 12.91.

*5-((2-((2R,3R,6R)-2-(3,4-Dichlorophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7ma**).* White solid; mp 150–151 °C; IR ($CHCl_3$): 3584.0, 2970.9, 2930.3, 1755.0, 1596.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.51 (m, 5H), 7.43–7.12 (m, 3H), 4.29 (d, J = 5.5 Hz, 1H), 3.51–3.47 (m, 1H), 2.87–2.82 (m, 1H), 2.26–2.23 (m, 1H), 1.78 (d, J = 12.0 Hz, 1H), 1.62–1.49 (m, 5H), 1.33 (s, 3H), 1.17 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.54, 142.65, 133.39, 132.25, 131.84, 130.08, 130.04, 130.01, 129.68, 129.57, 129.51, 129.48, 129.46, 129.45, 129.43, 127.45, 124.29, 124.25, 124.24, 124.22, 81.86, 74.09, 56.54, 46.70, 33.47, 27.85, 26.80, 26.60, 26.31, 21.70; MS (EI) m/z = 462 $[M]^+$, 463 $[M + H]^+$; Anal. Calcd for $C_{22}H_{24}Cl_2N_4OS$ C, 57.02; H, 5.22; N, 12.09. Found C, 57.25; H, 5.41; N, 11.88.

*5-((2-((2R,3R,6R)-2-(2-Bromophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7na**).* White solid; mp 115–117 °C; IR ($CHCl_3$): 3675.1, 3494.6, 3064.9, 2971.7, 2932.6, 1596.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51–7.46 (m, 5H), 7.42 (d, J = 7.0 Hz, 1H), 7.40–7.34 (m, 1H), 7.12–7.09 (m, 1H), 7.00–6.96 (m, 1H), 4.85 (d, J = 9.0 Hz, 1H), 3.55–3.51 (m, 1H), 3.09 (td, J = 9.0 Hz, 18.0 Hz, 1H), 2.33–2.29 (m, 1H), 1.79–1.74 (m, 1H), 1.67–1.63 (m, 1H), 1.57 (s, 3H), 1.53–1.48 (m, 1H), 1.30 (s, 3H), 1.15 (d, J = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.78, 141.64, 133.47, 132.43, 130.25, 129.87, 129.73, 129.42, 129.39, 129.36, 129.34, 129.31, 127.25, 124.17, 123.44, 80.30, 74.10, 57.41, 46.02, 33.56, 27.63, 27.28, 26.89, 21.83; MS (EI) m/z = 472 $[M]^+$, 473 $[M + H]^+$; Anal. Calcd for $C_{22}H_{25}BrN_4OS$ C, 55.81; H, 5.32; N, 11.83. Found C, 55.90; H, 5.46; N, 11.70.

*5-((2-((2R,3R,6R)-2-(4-Bromophenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)thio)-1-phenyl-1H-tetrazole (**7ra**).* White solid; mp 167 °C; IR ($CHCl_3$): 3583.7, 2930.5, 2858.0, 1595.5, 1498.1 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.51 (m, 3H), 7.35–7.33 (m, 4H), 7.18 (d, J = 6.5 Hz, 2H), 4.27 (d, J = 10.0 Hz, 1H), 3.51–3.47 (m, 1H), 2.83–2.78 (m, 1H), 2.27–2.23 (m, 1H), 1.79–1.76 (m, 1H), 1.62–1.52 (m, 2H), 1.47 (s, 3H), 1.29 (s, 3H), 1.17 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.61, 141.42, 133.46, 131.34, 131.21, 129.96, 129.78, 129.50, 129.45, 124.43, 121.90, 82.49, 74.02, 56.92, 53.34, 46.88, 33.62, 27.51, 26.85, 26.75, 21.76; MS (EI) m/z = 472 $[M]^+$, 473 $[M + H]^+$; Anal. Calcd for $C_{22}H_{25}BrN_4OS$ C, 55.81; H, 5.32; N, 11.83. Found C, 55.95; H, 5.53; N, 11.77.

*2-((2-((2R,3R,6R)-2-(4-Methoxyphenyl)-6-methyltetrahydro-2H-pyran-3-yl)propan-2-yl)thio)benzo[d]thiazole (**7cb**).* Slightly brownish solid; mp 100–102 °C; IR ($CHCl_3$): 3583.7, 3368.7, 2966.9, 2929.1, 2850.9, 1612.0, 1514.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.0 Hz, 1H), 7.45–7.42 (m, 2H), 7.35–7.29 (m, 2H), 6.84 (d, J = 5.0 Hz, 2H), 4.35 (d, J = 9.5 Hz, 1H), 3.77 (s, 3H), 3.57–3.51 (m, 1H), 2.46–2.40 (m, 1H), 1.80–1.68 (m, 3H), 1.62–1.41(m, 1H), 1.27 (s, 3H), 1.23 (s, 3H), 1.20 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.32, 159.32, 153.54, 136.28, 134.82,

129.22, 125.87, 124.72, 122.42, 120.71, 113.75, 113.34, 82.91, 74.04, 57.61, 55.15, 48.99, 34.02, 29.95, 27.52, 26.65, 21.90; MS (EI) m/z = 413 $[M]^+$, 414 $[M + H]^+$; Anal. Calcd for $C_{23}H_{27}NO_2S_2$ C, 66.79; H, 6.58; N, 3.39. Found C, 66.91; H, 6.69; N, 3.28.

*2-((2-((2R,3R,6R)-6-Methyl-2-(p-tolyl)tetrahydro-2H-pyran-3-yl) propan-2-yl)thio)benzo[d]thiazole (**7db**).* White solid; mp 107–108 °C; IR ($CHCl_3$): 3583.6, 3401.0, 2969.0, 2928.3, 2856.9, 1558.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.0 Hz, 1H), 7.42–7.39 (m, 1H), 7.31–7.27 (m, 3H), 7.10–7.09 (d, J = 8.0 Hz, 2H), 4.34 (d, J = 9.5 Hz, 1H), 3.55–3.49 (m, 1H), 2.48–2.42 (m, 2H), 2.29 (s, 3H), 1.77–1.66 (m, 2H), 1.48–1.40 (m, 1H), 1.27 (s, 3H), 1.20 (s, 3H), 1.17 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.42, 153.64, 139.64, 137.71, 137.68, 137.65, 129.27, 128.30, 128.07, 126.60, 126.56, 125.95, 122.96, 122.54, 120.74, 83.40, 74.08, 57.85, 48.93, 34.12, 30.17, 27.67, 26.55, 22.10, 22.08, 22.02, 21.32, 21.21; MS (EI) m/z = 397 $[M]^+$, 398 $[M + H]^+$; Anal. Calcd for $C_{23}H_{27}NOS_2$ C, 69.48; H, 6.85; N, 3.52. Found C, 69.57; H, 6.99; N, 3.43.

*(2R,3S,6R)-2-(4-Methoxyphenyl)-6-methyl-3-(prop-1-en-2-yl) tetrahydro-2H-pyran (**8**).*[13] Liquid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.60 (t, J = 11.0 Hz, 2H), 4.18 (dd, J = 10.5 Hz, 1H), 3.75 (s, 3H), 3.63–3.60 (m, 1H), 2.25–2.23 (m, 1H), 1.88–1.85 (m, 1H), 1.74–1.69 (m, 2H), 1.44–1.40 (m, 1H), 1.43 (s, 3H), 1.22 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); 158.81, 146.49, 133.62, 132.87, 129.45, 128.98, 128.69, 128.52, 128.51, 128.47, 113.59, 111.75, 83.56, 74.23, 55.08, 49.98, 33.52, 30.37, 22.10, 21.34, 21.09.

*((4-Methoxyphenyl)methylene)bis(p-tolylsulfane) (**9cc**).* Gummy liquid; IR ($CHCl_3$): 2952.3, 2835.1, 1608.3, 1509.0, 1491.3, 1251.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18–7.09 (m, 6H), 6.93 (d, J = 8.0 Hz, 4H), 6.67 (d, J = 8.5 Hz, 2H), 5.22 (s, 1H), 3.64 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.08, 137.82, 132.92, 131.89, 130.95, 129.53, 129.05, 113.65, 60.47, 55.18, 21.16.

Acknowledgements

The authors are grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial support under the Network Project CSC 130. The authors are thankful to Dr Sanjib Gogoi, Scientist, CSIR-NEIST for providing the NOESY spectrum. The authors also thank the Director, CSIR-NEIST for his continuous support and encouragement.

Notes and references

1 (*a*) J. Zhu and H. Bienayme, *Multicomponent reactions*, Wiely-VCH, Weinheim, 2005; (*b*) A. Padwa, *Pure Appl. Chem.*, 2004, **76**, 1933; (*c*) L. F. Tietze and N. Rackelmann, *Pure Appl. Chem.*, 2004, **76**, 1967; (*d*) K. Ablajan, W. Kamil, A. Tuoheti and S. Wan-Fu, *Molecules*, 2012, **17**, 1860; (*e*) For a review on "high order" MCRs, see: S. Brauch, S. S. V. Berkel and B. Westermann, *Chem. Soc. Rev.*, 2013, **42**, 4948; (*f*) R. C. Cioc, E. Ruijter and R. V. A. Orru, *Green Chem.*, 2014, **16**, 2958.

2 Reviews on multi-component reactions: D. B. Ramachary and S. Jain, *Org. Biomol. Chem.*, 2011, **9**, 1277.

3 (*a*) U. C. Reddy, B. R. Raju, E. K. P. Kumar and A. K. Saikia, *J. Org. Chem.*, 2008, **73**, 1628; (*b*) T. Yoshimitsu, T. Makino and H. Nagaoka, *J. Org. Chem.*, 2004, **69**, 1993; (*c*) M. A. Perry, S. D. Rychnovsky and N. Sizemore, *Synthesis of saturated oxygenated Heterocycles I, Topics in Heterocyclic Chemistry 35*, Springer-Verlag, Berlin Heidelberg, 2014; (*d*) Y. Y. Lin, M. Risk, S. M. Ray, D. V. Engen, J. Clardy, J. Golik, J. C. James and K. Nakanishi, *J. Am. Chem. Soc.*, 1981, **103**, 6773; (*e*) J. Lee, H. S. Oh and H. Y. Kang, *Tetrahedron Lett.*, 2015, **56**, 1099; (*f*) R. D. Norcross and I. Paterson, *Chem. Rev.*, 1995, **95**, 2041; (*g*) X. Tian, J. J. Jaber and S. D. Rychnovsky, *J. Org. Chem.*, 2006, **71**, 3176; (*h*) X.-F. Yang, M. Wang, Y. Zhang and C.-J. Li, *Synlett*, 2005, 1912.

4 (*a*) J. S. Yadav, B. V. S. Reddy, M. S. Reddy, N. Niranjan and A. R. Prasad, *Eur. J. Org. Chem.*, 2003, 1779; (*b*) S. R. Crosby, J. R. Harding, C. D. King, G. D. Parker and C. L. Willis, *Org. Lett.*, 2002, **4**, 577; (*c*) E. Arundale and L. A. Mikeska, *Chem. Rev.*, 1952, **51**, 505; (*d*) C. S. Barry, N. Bushby, J. R. Harding, R. A. Hughes, G. D. Parker, R. Roe and C. L. Willis, *Chem. Commun.*, 2005, 3727; (*e*) J. S. Yadav, B. V. S. Reddy, T. Maity and G. G. K. S. N. Kumar, *Tetrahedron Lett.*, 2007, **48**, 7155; (*f*) J. S. Yadav, B. V. S. Reddy, Y. S. Reddy, B. P. Reddy and P. A. Reddy, *Tetrahedron Lett.*, 2010, **51**, 1236; (*g*) F. Liu and T.-P. Loh, *Org. Lett.*, 2007, **9**, 2063; (*h*) U. C. Reddy, S. Bondalapati and A. K. Saikia, *Eur. J. Org. Chem.*, 2009, 1625; (*i*) G. Baishya, B. Sarmah and N. Hazarika, *Synlett*, 2013, 1137; (*j*) B. Sarmah, G. Baishya and R. K. Baruah, *Eur. J. Org. Chem.*, 2014, 7561; (*k*) B. B. Snider, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, ch. 2.1, vol. 2, p. 527; (*l*) K. N. Cossey and R. L. Funk, *J. Am. Chem. Soc.*, 2004, **126**, 12216; (*m*) D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, 661; (*n*) K. Meilert and M. A. Brimble, *Org. Lett.*, 2005, **7**, 3497; (*o*) J. S. Yadav, P. Rao, P. M. S. Reddy, N. V. Rao and A. R. Prasad, *Tetrahedron Lett.*, 2007, **48**, 1469.

5 (*a*) H. Kishino and K. Mikami, *J. Chem. Soc., Chem. Commun.*, 1993, 1843; (*b*) P. Saha, P. Gogoi and A. K. Saikia, *Org. Biomol. Chem.*, 2011, **9**, 4626; (*c*) D. A. Evans and J. Wu, *J. Am. Chem. Soc.*, 2005, **127**, 8006; (*d*) L. E. Overman, *Acc. Chem. Res.*, 1992, **25**, 352; (*e*) T.-P. Loh, L.-C. Feng and J.-Y. Yang, *Synthesis*, 2002, 937; (*f*) T. A. Blumenkopf, G. C. Look and L. E. Overman, *J. Am. Chem. Soc.*, 1990, **112**, 4399; (*g*) L. E. Overman and A. S. Thompson, *J. Am. Chem. Soc.*, 1988, **110**, 2248; (*h*) T.-P. Loh, J.-Y. Yang, L.-C. Feng and Y. Zhou, *Tetrahedron Lett.*, 2002, **43**, 7193; (*i*) S. Bondalapati, U. C. Reddy, P. Saha and A. K. Saikia, *Org. Biomol. Chem.*, 2011, **9**, 3428.

6 P. Saha, P. Ghosh, S. Sultana and A. K. Saikia, *Org. Biomol. Chem.*, 2012, **10**, 8730.

7 (*a*) G. Benz, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 6, p. 381; (*b*) C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, New York, 2nd edn, 1999, 1932; (*c*) S. Naik, G. Bhattacharjya, B. Talukdar and B. K. Patel, *Eur. J. Org. Chem.*, 2004, 1254; (*d*) A. R. Katritzky, H. Y. He and K. Suzuki, *J. Org. Chem.*, 2000, **65**, 8210; (*e*) A. R. Katritzky, C. Cai and S. K. Singh, *J. Org. Chem.*, 2006, **71**, 3375.

8 (*a*) L. I. Krimen and D. Cota, *J. Org. React.*, 1969, **17**, 213; (*b*) K. I. Bookes-Milburn, D. J. Guly, B. Lox and P. A. Procopin, *Org. Lett.*, 2003, **5**, 3313; (*c*) J. M. Concellon, E. Riego, J. R. Suarez, S. G. Grand and M. R. Diaz, *Org. Lett.*, 2004, **6**, 4499; (*d*) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 1948, **70**, 4045; (*e*) H. Plaut and J. J. Ritter, *J. Am. Chem. Soc.*, 1951, **73**, 4076; (*f*) J. J. Ritter and N. Y. Yonkers, *U.S. Patent*, 2573673, 1951.

9 (*a*) H. Fernholz and H. J. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 521; (*b*) K. L. Reddy, *Tetrahedron Lett.*, 2003, **44**, 1453; (*c*) J. C. Baum, J. E. Milne, J. A. Murry and O. R. Thiel, *J. Org. Chem.*, 2009, **74**, 2207.

10 (*a*) O. L. Epstein and T. Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 16480; (*b*) B. Sarmah, G. Baishya and R. K. Baruah, *RSC Adv.*, 2014, **4**, 22387; (*c*) M. Chiba, Y. Ishikawa, R. Sakai and M. Oikawa, *ACS Comb. Sci.*, 2016, **18**, 399.

11 (*a*) J. S. Yadav, B. V. S. Reddy, B. Anusha, U. V. S. Reddy and V. V. B. Reddy, *Tetrahedron Lett.*, 2010, **51**, 2872; (*b*) S. D. Rychnovsky and C. R. Thomas, *Org. Lett.*, 2000, **2**, 1217; (*c*) N. M. Nasir, K. Ermanis and P. A. Clarke, Review, *Org. Biomol. Chem.*, 2014, **12**, 3323; (*d*) C. Oleir, M. Kaafarani, S. Gastaldi and M. P. Bertrand, *Tetrahedron*, 2010, **66**, 413; (*e*) N. Ahmed and N. K. Konduru, *Beilstein J. Org. Chem.*, 2012, **8**, 177; (*f*) K. F. Chio, J. Warne, D. Gough, M. Penny, S. Green, S. J. Coles, M. B. Hursthouse, P. Jones, L. Hassall, T. M. McGuire and A. P. Dobbs, *Tetrahedron*, 2011, **67**, 5107.

12 (*a*) N. Hazarika and G. Baishya, *Eur. J. Org. Chem.*, 2014, 5686; (*b*) N. Hazarika, G. Baishya and P. Phukan, *Synthesis*, 2015, 2851.

13 B. Sarmah, G. Baishya, N. Hazarika and P. J. Das, *Synlett*, 2015, 2151.

14 T.-P. Loh, Q.-Y. Hu, K.-T. Tan and H.-S. Cheng, *Org. Lett.*, 2001, **3**, 2669.

15 O. O. Fadeyi, J. J. Mousseau, Y. Feng, C. Allais, P. Nuhant, M. Z. Chen, B. Pierce and R. Robinson, *Org. Lett.*, 2015, **17**, 5756 and reference cited therein.

16 (*a*) For review on biological acivities of mercaptobenzothiazole derivatives: M. A. Azam and B. Suresh, *Sci. Pharm.*, 2012, **80**, 789 and reference cited therein; (*b*) P. Saxena, D. C. P. Singh, A. Ali and V. Sharma, *Int. J. Pharm. Pharm. Sci.*, 2013, **5**, 454.

17 CCDC 1502070 contains the supplementary crystallographic data for compound **3n**.