Tetrahedron Letters 53 (2012) 762–764

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of novel annulated thiopyrano indole derivatives from simple oxindole via intramolecular 1,3-dipolar cycloaddition reactions of nitrone and nitrile oxide

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ARTICLE INFO

Article history:
Received 24 October 2011
Revised 28 November 2011
Accepted 29 November 2011
Available online 7 December 2011

Keywords:
Stereoselective synthesis
Isoxazolidine
Thiopyrano[2,3-*b*]indole
Oxindole
1,3-Dipolar cycloaddition reaction
β-Halo aldehyde

ABSTRACT

Synthesis of some novel isoxazolidine/dihydroisoxazole annulated thiopyrano[2,3-*b*]indole derivatives from simple oxindole via 1,3-dipolar cycloaddition reaction involving nitrone and nitrile oxide as 1,3-dipole is reported.

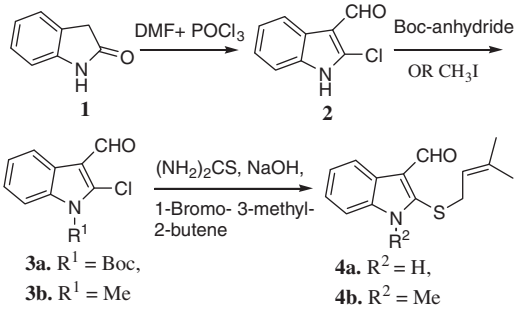
Indole nucleus is a prominent structural subunit present in numerous natural products and synthetic compounds with vital medicinal value.[1] Thiopyranoindole annulated heterocyclic compounds are important due to their biological activity.[2] Among the wide variety of heterocycles, dihydroisoxazoles/tetrahydroisoxazoles (isoxazolidines) are some very important and useful classes of compounds which are widespread in nature. Isoxazolidine derivatives possess antifungal,[3a] antiinflammatory,[3b] antimycobacterial[3c] and cytotoxic activity,[3d] and they also act as DNA intercalators.[3e]

1,3-Dipolar cycloaddition[4] of an alkene with nitrone and nitrile oxide is one of the reliable strategies for the construction of the dihydroisoxazoles/tetrahydroisoxazoles moieties. In fact, these structural units can be obtained through in situ formation of nitrile oxide/nitrone followed by 1,3-dipolar cycloaddition reaction sequence. For example, Oppolzer and co-workers reported the synthesis of benzopyran derivatives by intramolecular cycloaddition involving in situ nitrone preparation followed by the [3+2] cyclo addition reaction.[4f]

There are several examples of the synthesis of benzopyran and pyranobenzopyran moieties while those of their sulfur-containing analogues are rare.[5] A literature survey revealed that there are only a few reports on the synthesis of polycyclic pyranothio pyrans.[6] However, the interest in sulfur heterocycles of this class such as thiopyrans is growing because of the recent reports of their pharmacological and medicinal importance.[7] Hence, the development of new and facile synthetic methods for such heterocycles is considered to be of great significance.[8]

Recently, we have reported an efficient method for the synthesis of α-carbolines from oxindole by exploring three-component reaction in one-pot protocol.[9] As part of our continued interest on indole and the synthesis of diverse heterocyclic compounds of biological significance,[10] we report here the synthesis of some novel dihydroisoxazole/tetrahydroisoxazole annulated thiopyrano[2,3-*b*]indole derivatives from simple oxindole via intramolecular 1,3-dipolar cycloaddition reaction.

Oxoindole **1**, was taken as the starting material in our reaction strategy which on treatment with Vielsmeier reagent afforded the



Scheme 1.

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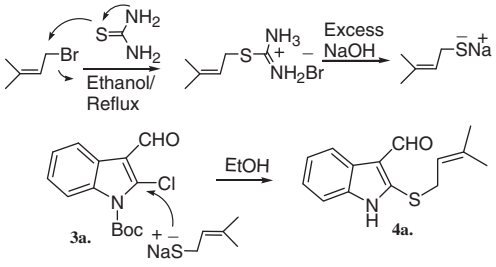
doi:10.1016/j.tetlet.2011.11.136

key β-halo aldehyde intermediate **2** (Scheme 1).[11] The indole nitrogen was readily protected by methyl iodide or di-*tert*-butyl dicarbonate (Boc_2O).[12] The unsaturated side chain could be smoothly introduced by substitution of chloro group from 2-chloro-3-formyl indole with prenyl thiolate.[13] For this nucleophilic substitution at the 2-position of the compound **3**, first prenyl thiolate was generated by the decomposition of *S*-prenyl isothiouronium salt with NaOH, to which *N*-protected 2-chloro-3-formyl indole **3** was added and refluxed for half an hour. After work-up, the *S*-alkenyl aldehyde **4** was obtained in a 70–72% yield where Boc was also deprotected (Scheme 1).[14] The nucleophilic substitution reaction did not occur in compound **2**.

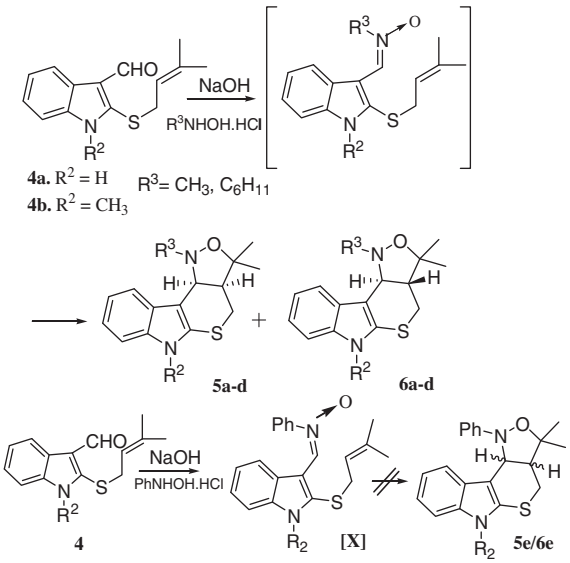
A plausible mechanism for the formation of indolo-*S*-alkenyl aldehyde **4** is outlined in Scheme 2. This type of Boc deprotection under basic conditions is well documented.[15]

First, we utilised nitrone as 1,3-dipole. In a simple experimental procedure, aldehyde **4a** was reacted with methylhydroxy amine hydrochloride in the presence of NaOH using ethanol as solvent under refluxing conditions (Scheme 3). To our expectation, intramolecular 1,3-dipolar cycloaddition reaction of nitrone occurred smoothly to give two isomers, **5a** (*cis*) and **6a** (*trans*) of tetrahydroisoxazolo[3′4′:4,5]thiopyrano[2,3-*b*]indole in 75% and 12% yields, respectively. The structures of **5a** and **6a** were determined from spectroscopic data and elemental analysis.[16] The stereochemistry was determined from the coupling constant of the H-**6b** and H-**9a** protons (for the *cis* isomer $J = 3.2$ Hz and for the *trans* isomer $J = 9.4$ Hz). The chemical shifts values of the *N*-Me protons at δ 2.90 and δ 2.85, respectively, as singlets further confirmed the involvement of the nitrone in the cycloaddition process. Both stereoisomers **5a** and **6a** exhibited strong molecular ion peaks $(M+H)^+$ at 275.5. Similarly, tetrahydroisoxazolo[3′,4′:4,5]thiopyrano[2,3-*b*]indole derivatives **5b–d** and **6b–d** were synthesised by utilising *N*-methylhydroxyamine hydrochloride and *N*-cyclohexyl hydroxyamine hydrochloride with **4a–b** (Table 1). It is noteworthy that although the nitrones form easily, the cycloaddition required forcing conditions (refluxing ethanol). Phenyl hydroxyl amine formed the nitrone [X] but has not given the cyclised product. The electron withdrawing nature of the aromatic group might have prevented the cyclisation. On the other hand the electron donating nature of the methyl and the cyclohexyl groups might have facilitated the cyclisation process to afford thiopyrano[2,3-*b*]indole derivatives **5** and **6**.

In order to prepare the dihydroisoxazolo[3′,4′:4,5]thiopyrano[2,3-*b*]indole, we first prepared oximes **7a** from **4a** by treatment with hydroxylamine hydrochloride in the presence of aqueous sodium hydroxide (Scheme 4).[17] The oximes on treatment with NaOCl in the presence of Et_3N at 0–20 °C afforded the desired dihydroisoxazolo[3′,4′:4,5]thiopyrano[2,3-*b*]indole **8a** in excellent yields via the formation of the nitrile oxides [A].[18] The structures of **8a** were determined from spectroscopic data and elemental analysis. Similarly compound **8b** was synthesised and characterised (Table 1).



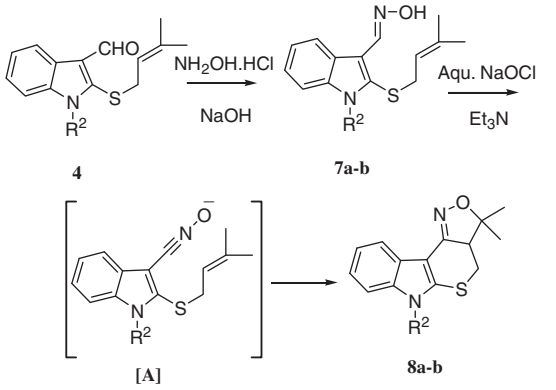
Scheme 2.



Scheme 3.

Table 1
Synthesis of novel tetrahydroisoxazole- and dihydroisoxazole fused thiopyrano[2,3-*b*]indole derivatives **5**, **6**, and **8**

Entry	Product	R^2	R^3	Mp (°C)	Yield (%)
1	**5a**	H	CH_3	157–158	75
2	**6a**	H	CH_3	149–150	12
3	**5b**	H	C_6H_{11}	135–136	73
4	**6b**	H	C_6H_{11}	127–128	8
5	**5c**	CH_3	CH_3	187–189	67
6	**6c**	CH_3	CH_3	183–184	7
7	**5d**	CH_3	C_6H_{11}	174–175	68
8	**6d**	CH_3	C_6H_{11}	171–172	8
9	**5e**	H	C_6H_5	–	NR
10	**6e**	CH_3	C_6H_5	–	NR
11	**8a**	H	—	167–168	65
12	**8b**	CH_3	—	184–185	62



Scheme 4.

In conclusion, we have reported the synthesis of several novel tetrahydroisoxazolo-, dihydroisoxazolo fused thiopyrano[2,3-*b*]indole from simple oxindole via intramolecular 1,3-dipolar cycloaddition reactions involving nitrones and nitrile oxides as 1,3-dipoles, in a regioselective manner. The present intramolecular 1,3-dipolar cycloaddition reaction strategy, which is the first application in the synthesis of tetrahydroisoxazole- and dihydroisoxazole fused thiopyranoindoles, can be further explored for the synthesis of various

fused heterocyclic compounds of biological importance. Further study of the reaction is in progress.

Acknowledgments

The authors thank DST, New Delhi for financial support. Mr. S. Majumder thanks CSIR for a research fellowship.

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14. A solution of 1-bromo-3-methyl-2-butene (2 mmol, 0.298 g), thiourea (3 mmol, 0.228 g) in ethanol (5 mL) was refluxed for 1 h. After addition of sodium hydroxide (10 mmol, 0.40 g) in ethanol (5 mL) the reaction was continued for an additional 1 h and then *N*-Boc protected 2-chloro-3-indolo carbaldehyde **3a** (2 mmol, 0.558 g) was added. The mixture was refluxed for half an hour and then water (10 mL) was added. The reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined extracts were dried over anhydrous sodium sulphate, the solvent evaporated and the residue was purified by column chromatography using petroleum ether–ethylacetate as eluent (7:3). **4a**. Yield: 0.352 g (72%), mp 114–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.70 (s, 3H), 3.45 (d, J = 8.04 Hz, 2H), 5.30–5.34 (m, 1H), 7.2–7.38 (m, 4H), 8.78 (s, br, 1H), 10.18 (s, 1H).
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16. To a solution of 2-thioprenyl-3-indolo carbaldehyde **4a** (2 mmol, 0.488 g) in 5 ml ethanol was added MeNHOH/HCl (3 mmol, 0.250 g) and the reaction mixture was set on reflux. NaOH (0.120 g, 3 mmol) was added portion-wise over a period of 5 min and refluxed for another 2 h. The solvent was removed under reduced pressure and the residue was purified by preparative TLC using ethyl acetate/hexane (4:6) as eluent to give **5a** and **6a**.
Compound **5a**: Yield: 0.411 g (75%), mp 157–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 6H), 2.90 (s, 3H), 3.15–3.29 (m, 1H), 3.86 (d, J = 3.2 Hz, 1H), 4.31–4.36 (m, 2H), 7.20–7.90 (m, 4H), 8.10 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.43 (2C), 29.56, 34.21, 66.51, 69.12, 106.49, 113.74, 119.82, 121.60, 126.02, 133.45 142.72, 148.15, 151.94. m/z [M+H]$^+$ 275.5. CHN analysis (calcd) C, 65.69; H, 6.56; N, 10.22; $C_{15}H_{18}N_2OS$ (found) C, 65.32; H, 6.48; N, 10.52.
Compound **6a**: Yield: 0.065 g (12%), mp 149–150 °C. 1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 6H), 2.85 (s, 3H), 3.22–3.31 (m, 1H), 3.90 (d, J = 9.4 Hz, 1H), 3.92–3.99 (m, 2H), 7.2–8.0 (m, 4H), 8.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.74 (2C), 28.98, 33.45, 65.48, 69.03, 105.66, 111.80, 118.32, 120.73, 124.40, 131.54, 139.76, 147.90, 151.04. m/z [M+H]$^+$ 275.5. CHN analysis (calcd) C, 65.69; H, 6.56; N, 10.22; $C_{15}H_{18}N_2OS$ (found) C, 65.20; H, 6.38; N, 10.58.
Compound **5b**. Yield: 0.499 g (73%), mp 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13–1.30 (m, 4H), 1.33 (s, 6H), 1.56–1.97 (m, 6H), 2.59–2.65 (m, 1H), 3.12–3.25 (m, 1H), 3.88 (d, J = 4.1 Hz, 1H), 4.25–4.38 (m, 2H), 7.17–7.93 (m, 4H), 8.10 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.52 (2C), 25.84 (2C), 27.56, 27.97 (2C), 29.82, 66.51, 67.89 70.45, 107.80, 112.52, 120.68, 122.84, 127.06, 134.94, 143.60, 149.18, 153.02. m/z [M+H]$^+$ 343.6. CHN analysis (calcd) C, 70.17; H, 7.60; N, 8.18; $C_{20}H_{26}N_2OS$ (found) C, 69.98; H, 7.64; N, 8.02.
Compound **6b**: Yield: 0.054 g (8%), mp 127–128 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ): δ 1.11–1.32 (m, 4H), 1.35 (s, 6H), 1.53–1.95 (m, 6H), 2.56–2.63 (m, 1H), 3.14–3.26 (m, 1H), 3.87 (d, J = 9.6 Hz, 1H), 4.22–4.33 (m, 2H), 7.16–7.91 (m, 4H), 8.18 (s, br,1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.34 (2C), 26.03 (2C), 28.53, 28.92 (2C), 30.64, 65.72, 68.35 70.58, 107.51, 111.80, 121.40, 122.21, 126.85, 133.43, 143.75, 147.91, 152.52. m/z [M+H]$^+$ 343.6. CHN analysis (calcd) C, 70.17; H, 7.60; N, 8.18; $C_{20}H_{26}N_2OS$ (found) C, 70.12; H, 7.01; N, 8.08.
Compound **5c**. Yield: 0.385 g (67%), mp 187–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 6H), 2.98 (s, 3H), 3.10–3.29 (m, 1H), 3.63 (s, 3H), 3.89 (d, J = 4.6 Hz, 1H), 4.29–4.41 (m, 2H), 7.22–7.78 (m, 4H), 8.23 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.57 (2C), 29.31, 36.76, 39.60, 66.29, 70.12, 108.74, 113.93, 118.58, 121.65, 126.73, 136.45, 144.30, 148.45, 152.86. m/z [M+H]$^+$ 289.7. CHN analysis (calcd) C, 66.66; H, 6.94; N, 9.72; $C_{16}H_{20}N_2OS$ (found) C, 66.54; H, 6.48; N, 9.82.
Compound **6c**: Yield: 0.040 g (7%), mp 183–184 °C. 1 H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 6H), 2.89 (s, 3H), 3.15–3.29 (m, 1H), 3.64 (s, 3H), 3.89 (d, J = 10.4 Hz, 1H), 4.18–4.35 (m, 2H), 7.19–7.88 (m, 4H), 8.29 (s, br,1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.53 (2C), 29.32, 35.86, 38.62, 67.54, 69.62, 107.98, 112.79 119.72, 121.50, 126.45, 135.57, 145.12, 146.58, 152.67. m/z [M+H]$^+$ 289.7. CHN analysis (calcd) C, 66.66; H, 6.94; N, 9.72; $C_{16}H_{20}N_2OS$ (found) C, 66.49; H, 6.61; N, 9.88. Compound **5d**: Yield: 0.484 g (68%), mp 174–175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12–1.33 (m, 4H), 1.34 (s, 6H), 1.57–1.98 (m, 6H), 2.53–2.68 (m, 1H), 3.13–3.26 (m, 1H), 3.64 (s, 3H), 3.88 (d, J = 4.8 Hz, 1H), 4.23–4.38 (m, 2H), 7.21–7.96 (m, 4H), 8.26 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.12 (2C), 25.46 (2C), 26.86, 27.24 (2C), 29.74, 35.89, 65.72, 67.71, 70.08, 107.48, 113.86, 119.48, 121.35, 127.96, 135.08, 145.59, 148.98, 154.14. m/z [M+H]$^+$ 357.8. CHN analysis (calcd) C, 70.78; H, 7.86; N, 7.86; $C_{21}H_{28}N_2OS$ (found) C, 70.65; H, 7.57; N, 8.02. Compound **6d**: Yield: 0.056 g (8%), mp 171–172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18–1.36 (m, 4H), 1.33 (s, 6H), 1.50–1.98 (m, 6H), 2.48–2.68 (m, 1H), 3.13–3.28 (m, 1H), 3.64 (s, 3H), 3.87 (d, J = 10.9 Hz, 1H), 4.28–4.39 (m, 2H), 7.19–7.99 (m, 4H), 8.22 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.14 (2C), 25.23 (2C), 26.41, 27.02 (2C), 30.01, 36.08, 65.68, 68.59, 70.12, 108.24, 112.89, 120.76, 121.29, 126.52, 134.71, 144.79, 147.99, 153.58. m/z [M+H]$^+$ 357.8 CHN analysis (calcd) C, 70.78; H, 7.86; N, 7.86; $C_{21}H_{28}N_2OS$ (found) C, 70.62; H, 7.61; N, 7.98.
17. Compound **4a** (2 mmol, 0.488 g) in 6 ml of EtOH was reacted with an aqueous solution of hydroxylamine prepared by adding NaOH (0.175 g in 4 ml H_2O) to a solution of NH_2OH/HCl (0.166 g, 2 mmol in 3 ml water), with stirring at room temperature. After 10 min, the solution was clear. The reaction mixture was allowed to stir at room temperature for 1 h after which the EtOH was evaporated and the compound was separated by extraction with dichloromethane. The organic extract was dried over anhydrous sodium sulphate and then evaporated under reduced pressure to obtain **7a**. Recrystallised from chloroform. Yield: 72%, mp 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 6H), 3.76 (d, J = 4.8 Hz, 2H), 5.96–6.05 (m, 1H), 7.24–7.68 (m, 4H), 8.15 (s, 1H), 8.46 (s, 1H). Compound **7b** was prepared similarly.
18. To a mixture of oxime **7a** (2 mmol, 0.518 g) and Et_3N (0.202 g, 2 mmol) in dichloromethane (8 ml), 10% aqueous NaOCl solution (3.5 ml) was added dropwise at −10 °C. The reaction mixture was allowed to stir for 1 h at room temperature. The organic phase was separated and the solvent was removed under reduced pressure. Product **8a** was purified by preparative TLC using EtOAc and hexane (7:3) as eluent. Yield: 0.335 g (65%), mp 167–168 °C. 1H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 6H), 2.68–2.89 (m, 1H), 3.26–3.35 (m, 1H), 3.73–3.94 (m, 1H), 7.20–7.75 (m, 4H), 8.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.06 (2C), 32.34, 56.28, 69.26, 112.52, 115.18, 119.58, 121.04, 122.89, 128.60, 129.37, 142.66, 157.29. m/z [M+H]$^+$ 259.4. CHN analysis (calcd) C, 65.11; H, 5.42; N, 10.85%; $C_{14}H_{14}N_2OS$ (found) C, 64.99; H, 5.32; N, 10.88%. Compound **8b**. Yield: 0.337 g (62%), mp 184–185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 6H), 2.69–2.92 (m, 1H), 3.23–3.37 (m, 1H), 3.63 (s, 3H), 3.72–3.95 (m, 1H), 7.23–7.77 (m, 4H), 8.39 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.12 (2C), 33.74, 36.78, 55.22, 69.69, 113.69, 115.84, 119.91, 121.58, 122.70, 127.25, 130.48, 143.74, 158.74. m/z [M+H]$^+$ 273.6. CHN analysis (calcd) C, 66.17; H, 5.88; N, 10.29; $C_{15}H_{16}N_2OS$ (found) C, 65.98; H, 5.64; N, 10.58.