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An expedient, regioselective synthesis of 2-alkylamino- and 2-alkylthiothiazolo[5,4-*e*]indoles

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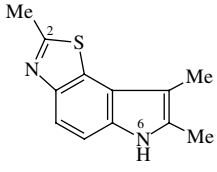
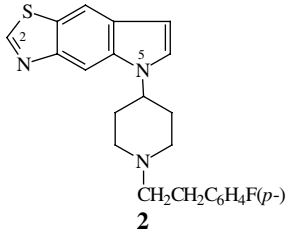
Abstract—1-Benzenesulfonyl-5-aminoindole **5**, prepared from 5-nitroindole **3**, was condensed with alkyl isothiocyanates and separately with carbon disulfide and alkyl bromides/iodides to furnish efficiently the corresponding *N*-alkyl-thioureidoindoles **6a**–**c** and the alkyl *N*-(indol-5′-yl)dithiocarbamates **9a**–**e**, respectively. Their cyclisation using *N*-bromosuccinimide (NBS) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), in the cold, followed by indolic *N*-deprotection, furnished regioselectively the 2-alkylamino- and the 2-alkylthiothiazolo[5,4-*e*]indoles **8a**–**c** and **11a**–**e**, respectively, in good overall yields.

Thiazoles are important heterocycles and continue to be synthetic targets because thiazolyl (hetero)arenes and several classes of annulated thiazoles display a diverse array of biological activities. The cruciferous phytoalexins, camalexins and spirobrassinins, are examples of thiazolyl heteroarenes,[1] whereas annulated thiazoles comprise the cytotoxic thiazoloquinazolines, -quinolines, -acridines, -acridones, 2-cyano-thiazolobenzodioxins, 2-(4-amino)phenyl- and 2-cyanobenzothiazoles and thiazolocarbazoles,[2] the cytotoxic thiazoloquinazolinones,[3] the antitumor and antitubercular thiazoloimidazoles,[4] the central dopamine agonists thiazoloindans and -benzopyrans,[5] the thiazolooxindole-based CDK-2 inhibitors[6] and the thiazolothiazepine-based HIV-1 integrase inhibitors.[7]

Motivated by the bioactive potential of annulated thiazoles, we have recently reported a new synthetic route to thiazolocarbazoles.[8] In continuation, we became interested in thiazoloindoles (TIs), only two isomeric types of which appear to have been synthesised up to now. Thus, for preparing polymethine dyes, 2,7,8-trimethylthiazolo[5,4-*e*]indole **1** was synthesised by the Fischer indole reaction of *N*-(2-methyl-6-benzothiazolyl)hydrazine with 2-butanone.[9] Later, in search of serotonin antagonists, the 5-substituted thiazolo[5,4-*f*]indole **2** was synthesised from 1-acetyl-6-aminoindoline in four steps in ca. 8% overall yield.[10] We became interested in developing a new synthetic route to the [5,4-*e*]-TI ring contained in **1**, in which we would construct the thiazole nucleus on the benzene ring of an indole, in contrast to the construction of the pyrrole nucleus on the benzene ring of a benzothiazole, as was used in the synthesis of **1**. As a result, we have been able to develop a new synthesis of 2-alkylamino- and 2-alkylthio[5,4-*e*]-TIs. Our successful findings are presented in this letter.



1



2

Our plan was to cyclise *N*-alkylthioureidoindoles. Accordingly, commercially available 5-nitroindole **3** was reduced (hydrazine hydrate, palladised charcoal, refluxing methanol)[11a] to 5-aminoindole (90%) which was then condensed with methyl isothiocyanate in

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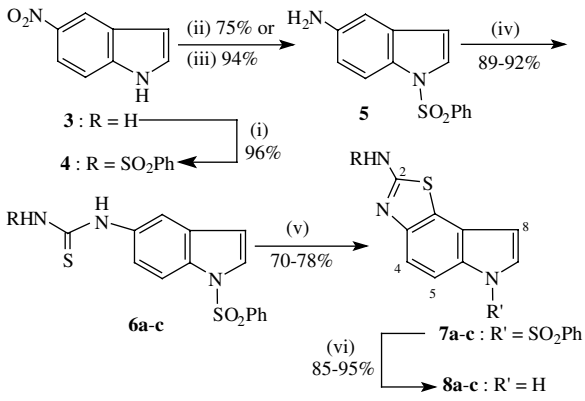
refluxing dry methanol to furnish 5-(*N*-methyl)thioureidoindole efficiently (92%). However, when we attempted cyclisation using bromine in acetic acid in the cold[12] or on montmorillonite K10 clay-*para*-toluenesulfonic acid (TsOH) at 60 °C,[8b] it underwent complete decomposition in both the cases. In order to overcome this difficulty, 5-nitroindole was first protected as its *N*-benzenesulfonyl derivative **4** (96%) and then reduced to the 5-amino derivative **5** by transfer hydrogenation using 10% palladised charcoal and either ammonium formate[11b] (75%) or hydrazine hydrate[11a] (94%). The amine **5** was then condensed separately with methyl, ethyl and benzyl isothiocyanates in refluxing dry methanol to give the respective 1-benzene-sulfonyl-5-(*N*-alkylthioureido)indoles **6a**–**c**[13] in ca. 90% yields. The conspicuous appearance of, (i) a ^{13}C NMR signal at δ 181–182 for the thiocarbonyl carbon, (ii) the peaks arising from the loss of H_2S (34 m.u.), RNH_2 (31/45/107 m.u.) and RNCS (73/87/149 m.u.) from the respective molecular ion-peaks in their mass spectra and (iii) supportive NMR and analytical data consolidated the structures of **6a**–**c**.

Since, in the case of thiazolocarbazoles, bromine in acetic acid had earlier been shown by us to lead to both angular and linear cyclisations and additionally to cause nuclear bromination,[8a] whereas clay-TsOH at 60 °C resulted in regioselective cyclisations,[8b] **6c**, as a representative substrate, was adsorbed on clay-TsOH and heated at 60 °C for a few hours, but unfortunately it remained completely unchanged.

Since, inter alia, NBS–DBU[14a] and NBS–Et_3N[14b] had been used previously for the cyclisation of the phytoalexin brassinin, an (indol-3′-yl)methyldithiocarbamate, to the corresponding indolothiazine, cylobrassinin, we decided to try NBS for the cyclisation of thioureido-(hetero)arenes to thiazolo(hetero)-arenes. Accordingly, each of **6a**–**c** was separately treated with NBS in dichloromethane at −10 °C and then with DBU, and the substrates cyclised rapidly and regioselectively to 6-benzenesulfonyl-2-alkylamino-thiazolo[5,4-*e*]indoles **7a**–**c** in good yields.[15] Subsequent indolic *N*-deprotection[16] using methanolic potassium carbonate furnished the 2-alkylaminothiazolo[5,4-*e*]indoles **8a**–**c**[17] in 48–62% overall yields starting from **3** (Scheme 1).

The appearance of two one-proton doublets at δ 7.25/7.39/7.27 and δ 7.20/7.32/7.20 (refer to H-4 and H-5, respectively, of the TI skeleton) with $J = 8.5$ Hz consolidated their angular structures, since the corresponding protons, H-4 and H-8, of the alternative linear [4,5-*f*]-TI structures would have appeared as one-proton singlets. Also, the shift of the ^{13}C NMR signals of C-8 from δ 108 in **7a**–**c** to ca. δ 100 in **8a**–**c** was a pointer to the cleavage of the *N*-benzenesulfonyl group.

This success prompted us to extend this methodology for a similar synthesis 2-alkylthiothiazoloindoles. Therefore, **5** was separately treated with carbon disulfide and each of methyl, ethyl, *n*-propyl, *n*-butyl and *i*-butyl bromides/iodides in the presence of pyridine and triethylamine to furnish efficiently, the respective alkyl

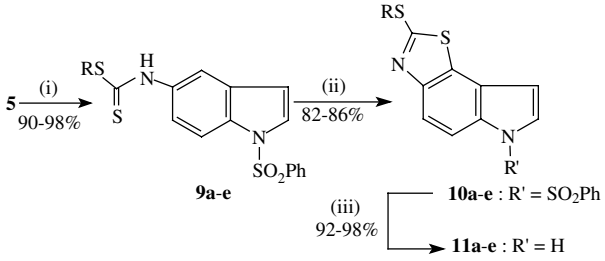


For **6-8** : R = Me (**a**), Et (**b**), CH_2Ph (**c**)

Scheme 1. Reagents and conditions: (i) NaOH, n-$Bu_4N^+HSO_4^-$, CH_2Cl_2, rt, 1 h, $PhSO_2Cl$, 3 h; (ii) HCO_2NH_4, 10% Pd–C, MeOH, reflux, 6–7 h; or (iii) $NH_2NH_2{\cdot}H_2O$, 10% Pd–C, MeOH, reflux, 3 h; (iv) RNCS (1.2 equiv), dry MeOH, reflux, 3–7 h; (v) NBS (1 equiv), CH_2Cl_2, −10 °C, 5–10 min, DBU (2 equiv), stir, 30 min; (vi) K_2CO_3 (4 equiv), MeOH–H_2O (3:1), reflux, 6–8 h.

N-(1′-benezensulfonylindol-3′-yl)dithiocarbamates **9a**–**e**.[18] The molecular weights of **9a**–**e** were determined from FAB-MS, which recorded peaks corresponding to (M+H), (M+H−H_2S) and (M+H−RSH), thereby additionally consolidating the presence of the alkyl dithiocarbamate side-chain in each of them. The appearance of the thiocarbonyl carbon at δ 197 for **9a** and δ 201 for **9b**–**e** in their ^{13}C NMR spectra lent additional support to the derived structures.

The cyclisation of **9a**–**e** by similar treatment with NBS–DBU, as in the cases of **6a**–**c**, furnished only the angularly cyclised products, viz 2-alkylthio-6-benzenesulfonylthiazolo[5,4-*e*]indoles **10a**–**e** in very good yields. In **10a**–**e**, the disappearance of the thiocarbonyl carbon signals and the appearance of signals at δ 164–165 were suggestive of cyclisations occuring. Also, the appearance of two one-proton, doublets at δ 7.8 and 8.0 with $J = 9$ Hz in **10a**–**e** demonstrated angular cyclisations. Subsequent indolic *N*-deprotection using methanolic potassium carbonate resulted in the smooth formation of the 2-alkylthiothiazolo[5,4-*e*]indoles **11a**–**e**[19] in 64–71% overall yields starting from **3** (Scheme 2). Cleavage



For **9-11**: R = Me (**a**), Et (**b**), *n*-Pr (**c**), *n*-Bu (**d**), *i*-Bu (**e**)

Scheme 2. Reagents and conditions: (i) CS_2 (1.2 equiv), Py–Et_3N, 0 °C, 30–45 min, RX (1.2 equiv; R = Br for **6d** and I for the remainder), 2–3 h; (ii) NBS (1 equiv), CH_2Cl_2, −10 °C, 5–10 min, DBU (2 equiv), stir, 30 min; (iii) K_2CO_3 (4 equiv), MeOH–H_2O (3:1), reflux, 6–8 h.

Table 1. Regioselective synthesis[a,b] of 2-alkylamino-TIs **8a–c** and 2-alkylthio-TIs **11a–e** starting from **5**

Thioureidoindoles	Time (h); yields (%)	*N*-SO_2 Ph-TIs	Yields (%)	2-Alkylamino-TIs	Yields (%)
6a	3.0; 90	**7a**	70	**8a**	85
6b	4.5; 92	**7b**	78	**8b**	95
6c	7.0; 89	**7c**	75	**8c**	90
Indolyldithiocarbamates	Yields (%)				
9a	95	**10a**	85	**11a**	98
9b	98	**10b**	82	**11b**	95
9c	93	**10c**	85	**11c**	94
9d	90	**10d**	86	**11d**	92
9e	90	**10e**	84	**11e**	96

[a] All products were identified by IR, ^{1}H and ^{13}C NMR, DEPT 135, MS, elemental analysis/HRMS, and in some cases additionally by HMQC and HMBC spectra.
[b] Refer to isolated pure products.

of the benzenesulfonyl groups was apparent from appropriate MS and NMR data, as well as from the lowering of the chemical shift of C-8 from δ 107–108 in **10a–e** to δ 101 in **11a–e**. A typical cyclisation procedure[15] and the yields of both types of condensation products as well as the TIs (Table 1) are presented.

In conclusion, we have developed an expedient and efficient five-step, regioselective synthesis of both 2-alkylamino- and 2-alkylthiothiazolo[5,4-*e*]indoles, which involves the construction of the thiazole nucleus on the benzene ring of precursor indoles. However, the bioactive potential of the synthesised TIs remains to be explored.

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15. General procedure for the cyclisation of **6a–c** to **7a–c** and **9a–e** to **10a–e**: To a solution of **6a–c/9a–e** (1 mM) in CH_2Cl_2 (10 mL) at −10 °C were added NBS (1 mM), and, after 5–10 min, DBU (2 mM). The solution was stirred for another 30 min, then poured into saturated aqueous $Na_2S_2O_3$ (15 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The pooled extracts were washed with water, dried (Na_2SO_4), the solvent removed in vacuo and the residue was purified either by crystallisation (for **10a**, **10b**) from CH_2Cl_2–petroleum ether, bp 60–80 °C or by column chromatogaphy over neutral alumina (for **7a–c**) (elution with 25–35% EtOAc in pet. ether) or over silica gel (for **10c–e**) (elution with 5–10% EtOAc in pet. ether).
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17. Data of a representative member, **8a**: mp 158–160 °C; IR (KBr): 3396, 3224, 3101, 1614, 1564, 1409, 761 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.90 (3H, d, J = 3 Hz),), 6.30 (1H, s), 7.20 and 7.25 (1H, d each, J = 8.5 Hz), 7.31 (1H, s), 7.51

(1H, br s), 11.13 (1H, s); ^{13}C NMR: δ 31.5 (CH_3), 99.8, 110.2, 113.9, 126.4 (all Ar–CH), 120.0, 121.7, 132.6, 146.8, 165.2 (all Ar–C); EI-MS: *m/z* 203 (M^+; 100%), 202, 188, 175, 174, 162, 161, 147. Anal. Calcd for $C_{10}H_9N_3S$: C, 59.11; H, 4.43; N, 20.69%. Found: C, 59.02; H, 4.42; N, 20.72%.

18. Data of a representative member, **9c**: mp 132–134 °C; IR (nujol): 1520, 1406, 1372, 1170, 1129, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.97 (3H, t, J = 7 Hz), 1.69 (2H, sextet, J = 7 Hz), 3.24 (2H, t, J = 7 Hz), 6.65 (1H, dd, J_1 = 4 Hz, J_2 = 1 Hz), 7.28 (1H, br d, J = 9 Hz), 7. 45 (2H, t, J = 7.5 Hz), 7.55 (1H, tt, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 7.60 (1H, d, J = 4 Hz), 7.62 (1H, br s), 7.89 (2H, dt, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 7.99 (1H, d, J = 9 Hz), 9.10 (1H, br); ^{13}C NMR: δ 13.4 (CH_3), 22.0, 38.2 (both CH_2), 109.1, 113.9, 118.3, 122.3, 126.7 (×2), 127.5, 129.3 (×2), 134.0 (all Ar–CH), 131.0, 133.4, 133.7, 138.0 (all Ar–C), 201.0 (C═S); FAB-MS: *m/z* 391 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}N_2O_2S_3$: C, 55.38; H, 4.61; N, 7.18%. Found: C, 55.31; H, 4.62; N, 7.20%.
19. Data of a representative member, **11c**: mp 90–92 °C; IR (KBr): 3436, 1620, 1411, 1353, 1191, 883, 788 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.08 (3H, t, J = 7.5 Hz), 1.86 (2H, sextet, J = 7 Hz), 3.30 (2H, t, J = 7 Hz), 6.61 (1H, s), 7.28 (1H, t, J = 2.5 Hz), 7.43 and 7.73 (1H, d each, J = 9 Hz), 8.68 (1H, s); ^{13}C NMR: δ 12.9 (CH_3), 22.3, 35.8 (both CH_2), 101.2, 109.8, 115.6, 124.2 (all Ar–CH), 120.1, 126.5, 132.1, 147.9, 161.5 (all Ar–C) EI-MS: *m/z* 248 (M^+), 233, 220, 215, 206 (100%), 174, 148; HR EI-MS: *m/z* 248.0434 (M^+). Calcd for $C_{12}H_{12}N_2S_2$: 248.0442.