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A clay-mediated, regioselective synthesis of 2-(aryl/alkyl)amino-thiazolo[4,5-*c*]carbazoles

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Abstract—The 3-aminocarbazoles **1a**–**e** were condensed with phenyl and benzyl isothiocyanates on montmorillonite K10 clay or TLC-grade silica gel at room temperature to furnish efficiently the *N*-phenyl and *N*-benzylthioureidocarbazoles, **2a**–**e** and **2f**, respectively, within minutes. When adsorbed on montmorillonite K10 clay impregnated with *para*-toluene sulfonic acid (1:1, w/w) and heated at 60–70 °C, **2a**–**e** and **2f** furnished the 2-anilino and 2-benzylaminothiazolo[4,5-*c*]carbazoles, **3a**–**e** and **3f**, respectively, regioselectively in high yields. The cyclisation was also effective for the *N*-methylthioureidocarbazoles **2g**–**i**.

The thiazole ring embodied in many recently synthesised thiazolyl compounds and condensed thiazoles with proven and potential bioactivities is an important pharmacophore. Some notable condensed thiazoles are the antitumour 2-(4-aminophenyl)benzothiazoles,[1] thiazolo[5,4-*a*]acridines,[2,3] 2-cyanobenzothiazoles,[4,5] thiazolo[5,4-*b*]quinolines,[6] imidazo[2,1-*b*]thiazoles,[7] 2-cyanothiazolobenzodioxins[8] and thiazolo[5,4-*f*]quinazolines.[9] In continuation of our recent efforts on the use of silica gel[10] and montmorillonite K10 clay[11–13] in the study of reactions of indoles and carbazoles, we became interested in developing a new synthesis of thiazolocarbazoles (TCs), which have been synthesised to date by three different routes.[14–17]

In the first route, 2-methyl-TCs were prepared by the Fischer indolisation of the phenylhydrazones of tetrahydrobenzo[*d*]thiazol-5/6-ones.[14] In the second route, cytotoxic 2-cyano-TCs were synthesised by thermolysis of 5-(*N*-carbazolylimino)-4-chloro-5*H*-1,2,3-dithiazoles.[15,16] In the third route, developed by us, 2-methylamino-TCs were prepared by cyclisation of 3-(*N*-methyl)thioureidocarbazoles by bromine in acetic acid.[17] In all three routes, both TCs and their precursors were prepared by carrying out the reactions in solution phase, and more importantly, both angular [4,5-*c*]-TCs and linear [5,4-*b*]-TCs were formed. Moreover, both 9-bromo angular TCs and 6-bromo linear TCs were additionally formed in our method. This complete lack of regioselectivity in the three extant routes to the TCs and the growing recognition of the environment-friendliness of clay-mediated reagents in organic synthesis[18] prompted us to develop a regioselective, two-step synthesis of 2-anilino/benzylamino[4,5-*c*]-TCs from 3-aminocarbazoles, which is presented in this communication. In both steps, we used montmorillonite K10 clay[19] as a crucial agent.

When a mixture of each of the 3-aminocarbazoles **1a**–**e**[20,21] and a stoichiometric equivalent of phenyl isothiocyanate was adsorbed on montmorillonite K10 clay at room temperature, the reaction was complete within 5 min in each case. Leaching of the clay with a suitable solvent furnished the corresponding 3-(*N*-phenyl)thioureidocarbazoles **2a**–**e** as the sole products in excellent yields. When montmorillonite K10 clay was replaced by TLC-grade silica gel, the same products were obtained in practically the same yields but required slightly longer periods, 10–15 min, perhaps because of the lower surface area and lower acidity of silica gel.[19] The diagnostic appearance of a ^{13}C NMR signal at around δ 180 (NH*C*SNH) and the appearance of peaks corresponding to the loss of 34 m.u. (H_2S), 93 m.u. ($PhNH_2$), 135 m.u. (PhNCS) and 151 m.u. (NHCSNHPh) from the

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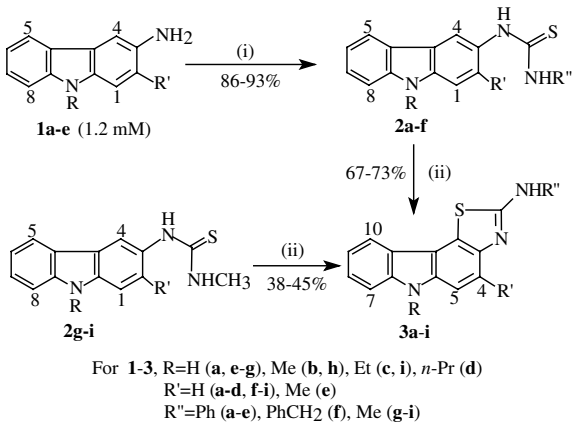
molecular-ion peaks in the mass spectra of **2a**–**e** in addition to the ^{1}H NMR signals expected of a 3-substituted carbazolyl group fully supported the structures of the thioureidocarbazoles **2a**–**e**.

When each of **2a**–**e** and 1.2 equivalent of *para*-toluene sulfonic acid (TsOH) were adsorbed on montmorillonite K10 clay and the resulting reactants-on-clay heated at 60–70 °C in an oven, compounds **2a**–**e** were consumed within 5–7 h. A simple work-up (vide experimental) furnished the 2-anilinothiazolo[4,5-*c*]carbazoles **3a**–**e**, that is, only the angular TCs as the sole products in very good yields (Scheme 1, Table 1).

Compared to **2a**–**e**, each of the TCs **3a**–**e** lacked two ^{1}H NMR signals (one NH and H-4) and two ^{13}C NMR signals ($\sim\delta$ 180: NH*C*SNH and $\sim\delta$ 117: CH-4) but exhibited, instead, two ^{13}C NMR signals ($\sim\delta$ 160: C-2 and $\sim\delta$ 122: C-10c), which constituted evidence in support of cyclisation. The appearance of two one-proton doublets (H-4,5) with *ortho*-couplings (*J* 8/8.5 Hz) at δ 7.62–7.66 in the ^{1}H NMR spectra of **3a**–**d** consolidated their angular structures, since each of the corresponding protons (H-4,10) in the alternative linear [5,4-*b*]-TCs would have appeared as a one-proton singlet. From the 2-methyl derivative **2e**, the formation of the angular TC **3e** was clearly the only possibility. Noticeably, the chemical shift of C-2 (δ 159–160) appeared to be typical of the 2-anilino angular TCs **3a**–**e**.



Scheme 1. Reagents and conditions: (i) PhNCS/PhCH$_2$NCS (1 mM), montmorillonite K10 clay (2 g), rt, <5 min or silica gel (2 g), rt, 10–15 min; (ii) TsOH (1.2 equiv), montmorillonite K10 clay (2 g), 60–70 °C, 5–7 h.

This two-step clay-mediated protocol also proved to be equally effective for a similar regioselective synthesis of the 2-benzylamino[4,5-*c*]-TC **3f** from **1a** via the corresponding thioureidocarbazole **2f**, prepared from **1a** by condensation with benzyl isothiocyanate.

This success prompted us to try this methodology for a similar regioselective synthesis of angular 2-methylamino-TCs **3g**–**i** via **2g**–**i**. However, the condensation of **1a**–**c** with an equivalent amount of methyl isothiocyanate failed to furnish any isolable products both on silica gel and on montmorillonite K10 clay. However, when **2g**–**i**, prepared by our earlier solution-phase method,[14] were separately adsorbed on montmorillonite K10 clay-TsOH (1:1.2) and heated at 60–70 °C as before, 2-methylaminothiazolo[4,5-*c*]carbazoles **3g**–**i**[17] were formed as the only products in moderate yields in comparable time periods (Scheme 1, Table 1).

In order to check the recyclability of montmorillonite K10 clay, the clay used in the conversion of **1c** to **2c** and left after leaching out of the products, was thoroughly washed with tetrahydrofuran, dried at 110–120 °C for 8 h and, after impregnation with TsOH used for the cyclisation of **2b** in the usual manner. The expected angular TC **3b** was obtained in 65% yield in the same time period (5 h) required when fresh clay was used. Montmorillonite K10 clay thus appeared to be reusable with the same degree of success at least for a second cycle.

To the best of our knowledge, the present method is the first regioselective synthesis of 2-(aryl/alkyl)aminothiazolo[4,5-*c*]carbazoles. We are now working on the synthesis of another class of condensed thiazoles using the present methodology.

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Table 1. Regioselective synthesis of 2-substituted [4,5-*c*]-TCs **3a**–**i**

Entry	3-NH$_2$-carbazoles (1 mM)	R″NCS (1.2 mM)	Thioureidocarbazoles[a]	Yields[b] (%)	2-Substd. TCs[c]	Time (h)	Yields[b] (%)
1	**1a**	PhNCS	**2a**	90	**3a**	7	73
2	**1b**	PhNCS	**2b**	93	**3b**	5	67
3	**1c**	PhNCS	**2c**[22]	90	**3c**[23]	6	69
4	**1d**	PhNCS	**2d**	86	**3d**	5	70
5	**1e**	PhNCS	**2e**	91	**3e**	6	73
6	**1a**	BnNCS	**2f**[d]	92	**3f**	6	67
7	—	—	**2g**[17]	—	**3g**	6	41
8	—	—	**2h**[17]	—	**3h**	5	38
9	—	—	**2i**[17]	—	**3i**	5	45

[a] **1a**–**e** and R″NCS adsorbed on montmorillonite K10 clay (2 g) and kept at room temperature for <5 min.
[b] Refer to yields of isolated pure products.
[c] From **2a**–**i** (1 mM) with TsOH (1.2 mM) on montmorillonite K10 clay (2 g) at 60–70 °C.
[d] Using PhCH$_2$NCS (1.2 mM).

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22. Preparation of **2a**–**f**. General procedure: A solution of **1a**–**e** (1 mM) in CH_2Cl_2 (2 mL) was mixed with a solution of PhNCS/$PhCH_2NCS$ (1.2 mM) in MeOH (0.2 mL), the resulting clear solution adsorbed on montmorillonite K10 clay (2 g) and the solvent allowed to evaporate off inside a fume-hood at room temperature. The reactants were consumed (TLC) within 5 min. The clay was then leached with CH_2Cl_2 (3 × 5 mL) and the solvent removed from the extract to furnish a residue, which was crystallised from petroleum ether (bp 60–80 °C)–CH_2Cl_2. All new compounds were identified by IR, ^1H (500 MHz) and ^{13}C (125 MHz) NMR, DEPT 135, EI-MS and elemental analysis or HR EI-MS. Data of a representative member **2c**: mp 114–116 °C; IR (Nujol): 3339, 3174, 1597, 1554, 738 cm^{-1}; MS: m/z 345 (M^+), 311, 252, 210 (100%), 194; ^1H NMR ($CDCl_3$): δ 1.43 (3H, t, $J = 7.0$ Hz), 4.35 (2H, q, $J = 7.0$ Hz), 7.22 (1H, t, $J = 9.0$ Hz), 7.24 (1H, t, $J = 7.5$ Hz), 7.36 (1H, d, $J = 7.5$ Hz), 7.37 (1H, d, $J = 8.0$ Hz), 7.39–7.46 (5H, m), 7.49 (1H, t, $J = 7.5$ Hz), 7.81 (1H, br s), 8.03 (1H, s), 8.05 (1H, d, $J = 8.0$ Hz), 8.16 (1H, br s); ^{13}C NMR: δ 14.2 (CH_3), 38.1 (CH_2), 109.2, 109.8, 119.1, 119.8, 121.1 (2×), 124.8, 125.5 (2×), 125.6, 126.9, 127.0 (all Ar–CH), 122.7, 124.0, 129.6, 129.9, 139.3, 140.9, 181.1 (all Ar–C). Anal. Calcd for C_{21} $H_{19}N_3S$: C, 73.04; H, 5.51; N, 12.17. Found: C, 73.26; H, 5.54; N, 12.13.
23. Cyclisation of **2a**–**i**. General Procedure: A solution of **2a**–**i** (1 mM) in CH_2Cl_2 (2 mL) was mixed with a solution of TsOH (0.23 g; 1.2 mM) in MeOH (0.2 mL) and adsorbed on montmorillonite K10 clay (2 g), the solvent was allowed to evaporate off (10–15 min) and the clay heated in an oven at 60–70 °C until the completion of the reaction (TLC). The clay was cooled, washed with water (3×3 mL) to get rid of excess TsOH and leached with THF (3 × 5 mL). The solvent extract was dried (Na_2SO_4), then evaporated and the resulting residue crystallised from EtOAc to furnish the TCs **3a**–**i**. All new compounds were identified as above. Data of a representative member **3c**: mp 218–220 °C; IR: 3223, 1600, 1546, 744 cm^{-1}; MS: m/z 343 (M^+; 100%), 328, 314, 255, 225, 163, 129, 105; ^1H NMR (d_6-DMSO): δ 1.31 (3H, t, $J = 6.8$ Hz), 4.49 (2H, q, $J = 7.0$ Hz), 6.99 (1H, t, $J = 7.0$ Hz), 7.29 (1H, t, $J = 7.25$ Hz), 7.36 (2H, t, $J = 7.5$ Hz), 7.49 (1H, t, $J = 7.5$ Hz), 7.62 (1H, d, $J = 8.5$ Hz), 7.66 (1H, d, $J = 8.0$ Hz), 7.78 (1H, d, $J = 8.5$ Hz), 7.83 (2H, d, $J = 7.5$ Hz), 7.90 (1H, d, $J = 7.5$ Hz), 10.49 (1H, s); ^{13}C NMR: δ 14.6 (CH_3), 38.1 (CH_2), 108.4, 110.3, 118.2 (×2), 118.5, 119.9, 121.3, 122.5, 126.4, 129.8 (×2) (all Ar–CH), 115.4, 121.3, 122.0, 136.9, 140.4, 141.8, 146.7, 159.9 (all Ar–C); HRMS: m/z 343.1146 (M^+). Calcd for $C_{21}H_{17}N_3S$: 343.1137.