First synthesis of bis[1,2,3]triazolo[1,5-*b*;5′,1′-*f*][1,3,6]thiadiazepine derivatives by [2+1] condensation of 1,2,3-thiadiazoles with vicinal diamines

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Novel bistriazolo[1,3,6]thiadiazepine derivatives have been prepared by the base-catalyzed condensation of aromatic and aliphatic 1,2-diamines with 5-chloro-1,2,3-thiadiazoles, *via* a multistep process which is thought to involve two Dimroth rearrangements and subsequent loss of hydrogen sulfide by intramolecular nucleophilic substitution.

Seven-membered rings fused with azoles are of special interest as biologically active compounds due to their structural similarity to benzodiazepine tranquilizers and to the aglycon of coformycin nucleoside antibiotics.[1] Despite a large number of papers devoted to various seven-membered heterocycles containing oxygen and nitrogen there are only a few dealing with sulfur containing compounds of this type.[2] We report here a very efficient synthesis of a novel ring system, ditriazolothiadiazepine.

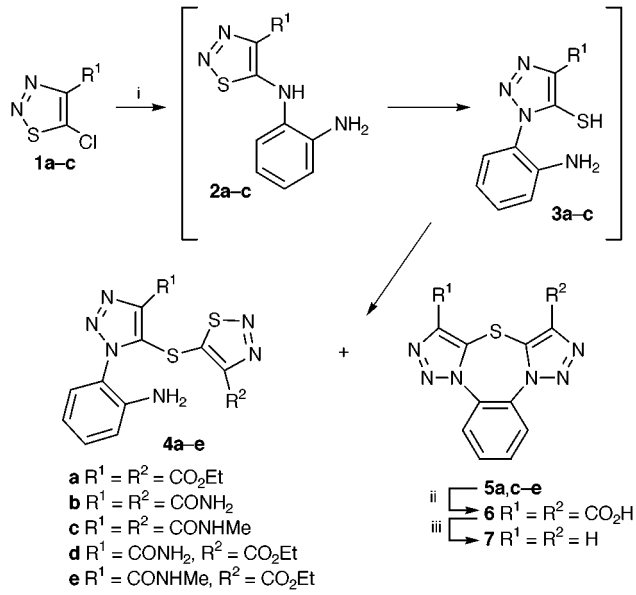
5-Halo-1,2,3-thiadiazoles, when substituted in the 4-position by an electron-withdrawing group, will on reaction with amines undergo a Dimroth rearrangement,[3] and the resulting 5-mercaptotriazoles can react with a second equivalent of thiadiazole to afford 5-(1,2,3-triazol-5-ylsulfanyl)-1,2,3-thiadiazoles.[4] We decided to apply this reaction to 5-chlorothiadiazole ester **1a** and 1,2-phenylenediamine (Scheme 1). We found the outcome of the reaction to be dependant on both reaction time and the presence of Et_3N catalyst. Without catalyst, the only product from the reaction of phenylenediamine and 2 equiv. of **1a** (EtOH, reflux) is the expected [2+1] adduct **4a**. In the presence of 1 equiv. of phenylenediamine, 2 equiv. of **1a** and 3 equiv. of Et_3N, a 2:1 mixture of **4a** and the unexpected bistriazolo[1,5-*b*;5′,1′-*f*][1,3,6]thiadiazepine derivative **5a** was isolated after 3 h reflux in EtOH. Prolonged heating of the reaction mixture gave **5a** as the sole product in 70% yield. Therefore it seemed logical to assume that sulfide **4a** was an intermediate in the formation of **5a**. This fact was confirmed by heating of isolated **4a** with Et_3N in EtOH, which also gave **5a**. The highly symmetrical structure of **5a** was immediately apparent from its ^1H and ^{13}C NMR spectroscopic data.[5]

On the other hand, the 5-chloro-1,2,3-thiadiazole amides **1b**,**c** gave only the sulfides **4b**,**c**, which did not transform to the corresponding fused thiadiazepines **5b**,**c**, even on prolonged heating in the presence of Et_3N. This behaviour is probably the result of the lower reactivity of the thiadiazole 5-carbon of **4b**,**c** towards intramolecular nucleophilic attack. The sulfides **4d**,**e** could be prepared from **2b**,**c** and **1a** in the presence of Et_3N, and cyclized to the unsymmetrically substituted thiadiazepines **5d**,**e**. The compounds **2b**,**c** were prepared from a 2:1 mixture of phenylenediamine and **1b**,**c** in DMF without the addition of Et_3N.

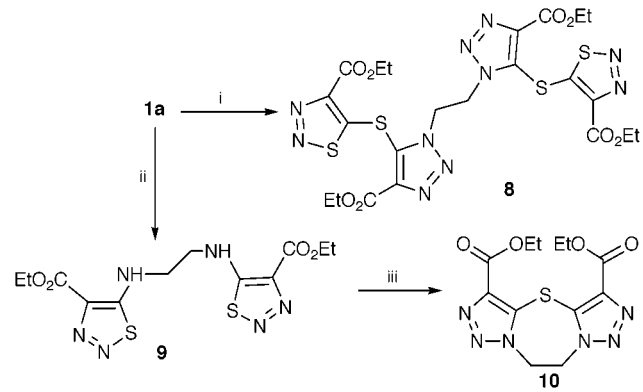
The parent ring system **7** could be prepared by saponification of diester **5a**, followed by the smooth decarboxylation of the diacid **6** by heating the melt at 180 °C. Again, the highly symmetrical structure is apparent from the ^1H and ^{13}C NMR spectroscopic data.[5] The bisamide **5c**, which is not accessible directly from phenylenediamine and **1c**, has been prepared in good yield from **5a** by condensation with excess $MeNH_2$.

The aliphatic 1,2-diaminoethane was reacted with chloroester **1a** (Scheme 2). Again, the outcome of the reaction was dependant on the reaction circumstances. Using the same conditions as above (Et_3N, EtOH, reflux) gave the [4+1] adduct **8** in 60% yield. On the other hand, the reaction of **1a** and ethylenediamine at reflux temperature in $CHCl_3$ gave the bisadduct **9**. Interestingly, **9** rearranged in EtOH with the formation of thiadiazepine **10** when refluxed in the presence of 3 equiv. of Et_3N.

From these results we can conclude that aliphatic amines are more reactive towards the chloroester **1a**. Moreover, the subsequent Dimroth rearrangement of **9** goes faster because the



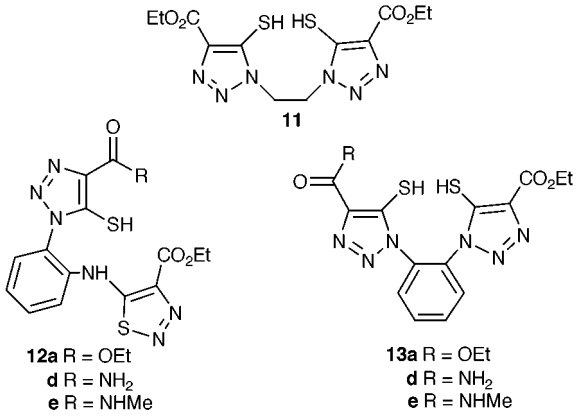
Scheme 1 *Reagents and conditions*: i, Et_3N, EtOH, reflux; ii, NaOH, then HCl; iii, 180 °C.



Scheme 2 *Reagents and conditions*: i, EtOH, $H_2NCH_2CH_2NH_2$, reflux; ii, $CHCl_3$, $H_2NCH_2CH_2NH_2$; iii, Et_3N, EtOH, reflux.

resulting *N*-alkyltriazole **11** is more stable than the corresponding *N*-aryltriazole **13**.[6]

We can argue that in both cases, either with aliphatic or aromatic amines, bisthiols of types **11** and **13** are formed, which



can react *via* an intra- or inter-molecular nucleophilic substitution. For ethylenediamine the bisthiol **11** is formed from **9** by two Dimroth reactions. For aryldiamines the Dimroth reaction of monoadducts **2a**–**c** takes place before the second substitution reaction, with the formation of thiols **3a**–**c**, which are not isolated but immediately react with a second equivalent of 5-chlorothiadiazoles **1a**–**c** to afford **4a**–**c**. Compounds **4d**,**e** are formed in a similar way from **1a** and **2b**,**c**. The 1,2,3-thiadiazole rings of **4a**,**d**,**e** are electron-poor enough to activate for intramolecular amine substitution, and thiols **12a**,**d**,**e** are formed, which undergo fast Dimroth rearrangement to dithiols **13a**,**d**,**e**. Finally, hydrogen sulfide is lost from dithiols **11** or **13a**,**d**,**e** by another intramolecular nucleophilic substitution, yielding thiadiazepines **10** or **5a**,**d**,**e**.

The intramolecular nucleophilic substitution of dithiol **11** is slower because of the more electron-rich and hence less reactive *N*-alkyltriazole, and will only occur if no intermolecular reactions with 5-chlorothiadiazole are possible, *e.g.* on isolated **9**. Otherwise, the [4+1] adduct **8** is obtained. Another, perhaps even more important reason why the intramolecular nucleophilic substitution of **11** is slow can be found in the larger degree of freedom of the flexible ethylene as compared to the rigid 1,2-phenylene group. Indeed, **11** is likely to exist mainly in a conformation with the two heterocyclic thiol groups widely separated.

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5 *Selected data* for **5a**: mp 164 °C, δ_H($CDCl_3$) 1.48 (6H, t, *J* 7.1, CH_3), 4.51 (4H, q, *J* 7.1, CH_2), 7.79–7.81 (2H, m, CH-arom), 8.08–8.11 (2H, m, CH-arom); δ_C($CDCl_3$) 14.2 (CH_3), 62.1 (CH_2), 126.3 (4,5 CH arom.), 128.2 (1,2-C arom.), 131.4 (3,6 CH arom.), 134.5 (C-5 triazole), 139.7 (C-4 triazole), 159.2 (CO); *m*/*z* 386 ($M^{+\cdot}$, 25), 258 ($M^{+\cdot} - CO_2Et - 2N_2$, 83), 214 ($M^{+\cdot} - 2CO_2Et - N_2$, 71), 186 ($M^{+\cdot} - 2CO_2Et - 2N_2$, 100) (calcd. for $C_{16}H_{16}N_6O_4S$: C, 49.74; H, 3.65; N, 21.75; S, 8.30. Found: C, 49.33; H, 3.99; N, 21.59; Sl 8.32%). For **7**: mp 253 °C; δ_H(DMSO-d_6) 7.87–7.94 (2H, m, CH-arom.), 8.06–8.14 (2H, m, CH-arom.), 8.17 (2H, s, 2CH); δ_C(DMSO-d_6) 126.1 (4,5-CH arom.), 127.8 (C5 triazole), 130.0 (1,2-C arom.), 131.3 (3,6-CH arom.), 135.6 (C4 triazole); *m*/*z* 242 ($M^{+\cdot}$, 61), 186 (M+. − $2N_2$, 100), 102 ($C_7H_4N^+$, 76), 76 ($C_6H_4^{+\cdot}$, 52) (calcd. for $C_{10}H_6N_6S$: C, 49.58; H, 2.50; N, 34.69; S, 8.30. Found: C, 49.68; H, 2.81; N, 34.43; S, 8.32%).

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