Use of tandem A_N-A_N reactions for the synthesis of thiazolo[4,5-*e*]-1,2,4-triazines

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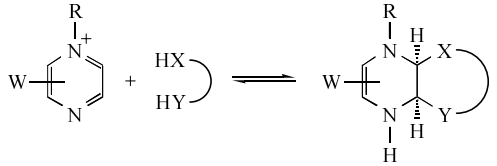
3-Aryl-1,2,4-triazines react with thioamides in acetic anhydride to produce thiazolo[4,5-*e*]-1,2,4-triazine derivatives and this reaction represents a new method for the fusion of thiazole and 1,2,4-triazine rings based on the nucleophilic *ortho*-diaddition type (A_N-A_N) cyclization reactions.

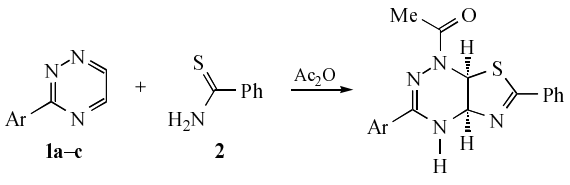
The *ortho*-diaddition type (A_N-A_N) cyclizations of π-deficient aza-aromatics (pyridazines, pyrazines, 1,2,4-triazines, pyrido[2,3-*b*]-pyrazines, pteridines, their quaternary salts, aza and benzo analogues, *etc*.) with bifunctional nucleophiles are of interest as an effective methodology for the synthesis of condensed heterocyclic systems.[1–7] A general scheme for the synthesis of condensed tetrahydropyrazines from pyrazinium cations is given below.



Scheme 1

Several examples of the tandem A_N-A_N reactions between 1,2,4-triazinium salts and bifunctional nucleophiles have been reported;[3–5,8–10] however, the patterns of heterocyclic fragments annelated to the 1,2,4-triazine ring are rather limited. Due to the relatively low stability of tetrahydrotriazines, only two types of condensed systems, *i.e.*, pyrrolo[2,3-*e*]- and furo[2,3-*e*]-1,2,4-triazines, have so far been obtained by the reactions of 1,2,4-triazinium salts with acetoacetamides,[3,8,9] ketene-*N*,*N*′-aminals,[10] and other C,N- or C,O-dinucleophiles.[5] It should be noted that all ring systems hitherto annelated in this way to 5,6-unsubstituted 1,2,4-triazines are heterocycles bearing one heteroatom, so that at least one of the two newly formed bonds in the fused tetrahydrotriazine systems is a C–C bond, enhancing the stability of the adducts. The *ortho*-diaddition reactions of 1,2,4-triazinium salts with bifunctional nucleophiles in which both reactive centres are heteroatoms have never, so far, resulted in the formation of stable adducts.

In this paper, we report the first successful examples of the tandem *ortho*-diaddition type cyclization reaction between 1,2,4-triazines and N,S-dinucleophiles. We found that the reaction of 5,6-unsubstituted 3-aryl-1,2,4-triazines **1a–c** with thiobenzamide **2** in acetic anhydride proceeds very smoothly at room temperature resulting in the formation of thiazolo[4,5-*e*]-1,2,4-triazines **3a–c** in good yields.† The use of acetic anhydride as a solvent in this reaction is very important since the N-acetylation of adducts enhances their stabilty.



1a–c **2** **3a–c**

a Ar = Ph
b Ar = *p*-$MeOC_6H_4$
c Ar = *p*-$NO_2C_6H_4$

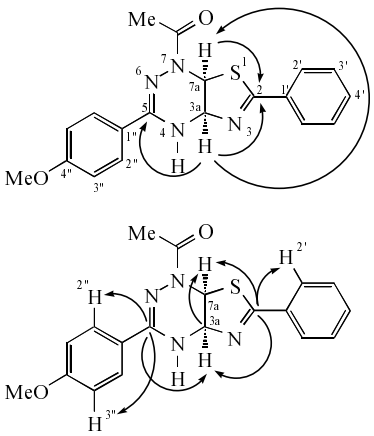
Scheme 2

The elemental analytical data and the molecular ion (M^+) peaks in the mass spectra of compounds **3a–c** are in full agreement with the 1:1 adduct formation.

Evidence for the structure of **3a–c** is provided by ^1H and ^{13}C NMR, including proton-coupled spectra, as well as HETCOR and HMBC two-dimensional heteronuclear experiments performed for compound **3b**.

In the ^1H NMR spectra of thiazolotriazines **3a–c**, the ring junction proton 7a-H appears as a doublet (δ 6.36–6.46 ppm) with $^3J_{7a\text{-}H,\ 3a\text{-}H}$ 7.5–7.7 Hz, while the resonance signal of 3a-H (δ 6.15–6.19 ppm) is a double doublet due to additional coupling with the adjacent NH proton: $^3J_{3a\text{-}H,\ NH}$ 2.1–2.2 Hz. The values of the vicinal coupling constants $^3J_{7a\text{-}H,\ 3a\text{-}H}$ 7.5–7.7 Hz correspond to the *cis* orientation of the ring junction protons, which is a common feature of tetrahydropyrazines and tetrahydro-1,2,4-triazines annelated with five-membered heterocycles.[11]

In the ^{13}C NMR spectra of **3a–c**, the ring junction carbon atoms 3a-C and 7a-C can easily be distinguished due to a considerable gap in their chemical shifts and the difference in one-bond C–H coupling constants. According to the ^{13}C NMR spectral data on the related system of 3a,4,9,9a-tetrahydrothiazolo-[4,5-*b*]quinoxalines, the ring junction carbon atom 3a-C adjacent to the C=N bond of the thiazole ring resonates at a lower field (93–97 ppm) and has a smaller one-bond coupling constant ($^1J_{C,\ H}$ 154–157 Hz) relative to the corresponding parameters of the ring junction carbon 9a-C adjacent to sulfur (67–70 ppm, $^1J_{C,\ H}$ 164–167 Hz).[11–13] Indeed, in the ^{13}C NMR spectra of **3a–c**, the resonance signal of 3a-C is observed at a lower field (δ 80.71–80.79 ppm, $^1J_{3a\text{-}C,\ 3a\text{-}H}$ 160.8–162.1 Hz), while the 7a-C resonates at 61.29–62.06 ppm and is coupled with 7a-H ($^1J_{7a\text{-}C,\ 7a\text{-}H}$ 166.8–168.9 Hz). These data provide unequivocal evidence for the regio-orientation of the thiazole ring. The position of NH (and therefore the site of the *N*-acetyl group) is clear from two vicinal couplings: $^3J_{3a\text{-}H,\ NH}$ and $^3J_{3a\text{-}H,\ 5\text{-}C}$. Long-range couplings observed in the HMBC spectrum of **3b** (Scheme 3, Table 1) are also in full correspondence with the structure.



Scheme 3 Indicative long-range interactions in the HMBC spectrum of **3b**.

Table 1 Long-range correlations observed in the HMBC spectrum of **3b**.

Cross-section along F1		Cross-section along F2	
Proton	Correlated carbon	Carbon	Correlated proton
2″-H	4″-C, 5-C	C=O	Me
4′-H	2′-C	2-C	2′-H, 7a-H, 3a-H
2′-H	2-C, 4′-C	4″-C	2″-H, 3″-H, OMe
3′-H	1′-C	5-C	2″-H, 3″-H, 3a-H
3″-H	4″-C, 1″-C	1′-C	3′-H
7a-H	2-C	4′-C	2′-H, 3′-H
3a-H	2-C, 5-C, 7a-C	3′-C	4′-H, 2′-H
OMe	4″-C	2′-C	4′-H, 3′-H
Me	C=O	1″-C	3″-H
		3″-C	2″-H
		3a-C	7a-H

† The ^{1}H NMR spectra in [$^2H_6$]DMSO were recorded on a Bruker WP-250 instrument (250 MHz for ^{1}H). The ^{13}C NMR spectra of **3a–c** in $CDCl_3$ were measured on a Bruker DRX-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Mass spectra were recorded using a Varian MAT 311A spectrometer.

Typical procedure for the prepararion of **3a–c**. Thiobenzamide (2.70 mmol) was added to a suspension of 3-aryl-1,2,4-triazines **1a–c** (2.70 mmol) in 2 ml (in case of **1c**, in 25 ml) of acetic anhydride. The reaction mixture was stirred at room temperature for 6 h (in case of **3c**, for 3 days). The precipitate obtained was filtered off and washed with a small amount of acetic anhydride and hexane (in case of **3c**, with isopropanol) and dried in air.

For **3a**: yield 58%, mp 206–207 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 2.28 (s, 3H, Me), 6.18 (dd, 1H, 3a-H, $^3J_{3a\text{-}H,\ 7a\text{-}H}$ 7.7 Hz, $^3J_{3a\text{-}H,\ NH}$ 2.2 Hz), 6.46 (d, 1H, 7a-H, $^3J_{7a\text{-}H,\ 3a\text{-}H}$ 7.7 Hz), 7.4–7.6 (m, 6H, 2Ph), 7.7–7.8 (m, 2H, Ph), 7.8–7.9 (m, 2H, Ph), 8.48 (d, 1H, NH, $^3J_{NH,\ 3a\text{-}H}$ 2.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.37 (q, Me, *J* 129.2 Hz), 62.06 (dd, 7a-C, *J* 168.2 Hz, *J* 4.0 Hz), 81.00 (d, 3a-C, *J* 160.8 Hz), 126.41 (dt, *J* 160.8 Hz, *J* 6.7 Hz), 128.00 (dt, *J* 161.2 Hz, *J* 6.7 Hz), 128.45 (dd, *J* 161.3 Hz, *J* 7.5 Hz), 128.84 (dd, *J* 161.8 Hz, *J* 6.7 Hz), 130.30 (dt, *J* 161.0 Hz, *J* 8.3 Hz) and 132.08 (dt, *J* 161.5 Hz, *J* 8.4 Hz) (6 aromatic CH carbon atoms of two phenyl groups), 132.79 (t, 1′-C, Ph, *J* 7.9 Hz), 133.08 (t, 1″-C, Ph, *J* 6.9 Hz), 146.14 (m, 5-C), 167.31 (dt, 2-C, $J_d \approx J_t$ 4.9 Hz), 170.48 (q, C=O, *J* 6.4 Hz). MS, *m*/*z* (%): 336 (83) [M$^+$], 173 (33), 158 (22), 157 (43), 121 (34), 104 (100), 103 (23), 77 (28). Found (%): C, 64.27; H, 4.93; N, 16.87. Calc. for $C_{18}H_{16}N_4OS$ (%): C, 64.27; H, 4.79; N, 16.65.

For **3b**: yield 51%, mp 172–173 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 2.26 (s, 3H, Me), 3.80 (s, 3H, OMe), 6.15 (dd, 1H, 3a-H, $^3J_{3a\text{-}H,\ 7a\text{-}H}$ 7.7 Hz, $^3J_{3a\text{-}H,\ NH}$ 2.1 Hz), 6.46 (d, 1H, 7a-H, $^3J_{7a\text{-}H,\ 3a\text{-}H}$ 7.7 Hz), 7.00 (d, 2H, C_6H_4OMe, *J* 8.8 Hz), 7.4–7.6 (m, 3H, Ph), 7.7–7.8 (m, 2H, Ph), 7.80 (d, 2H, C_6H_4OMe, *J* 8.8 Hz), 8.38 (d, 1H, NH, $^3J_{NH,\ 3a\text{-}H}$ 2.1 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.22 (q, Me, *J* 129.6 Hz), 55.27 (q, OMe, *J* 144.2 Hz), 61.29 (ddd, 7a-C, *J* 166.8 Hz, *J* 4.4 Hz, *J* 1.4 Hz), 80.71 (dd, 3a-C, *J* 162.1 Hz, *J* 0.9 Hz), 113.88 (dd, 3″-C, C_6H_4OMe, *J* 160.4 Hz, *J* 5.1 Hz), 125.12 (t, 1″-C, C_6H_4OMe, *J* 7.5 Hz), 127.20 (dd, 2″-C, C_6H_4OMe, *J* 159.9 Hz, *J* 7.0 Hz), 128.03 (ddd, 2′-C, Ph, *J* 160.6 Hz, *J* 7.4 Hz, *J* 6.4 Hz), 128.49 (dd, 3′-C, Ph, *J* 162.1 Hz, *J* 7.9 Hz), 132.01 (dt, 4′-C, Ph, *J* 164.5 Hz, *J* 7.2 Hz), 132.55 (t, 1′-C, Ph, *J* 7.8 Hz), 145.89 (dt, 5-C, *J* 3.7 Hz), 161.35 (dqt, 4″-C, C_6H_4OMe, *J* 4.8 Hz, *J* 6.8 Hz, *J* 2.4 Hz), 171.38 (dt, 2-C, $J_d \approx J_t$ 5.2 Hz), 171.62 (qd, C=O, *J* 6.4 Hz, *J* 0.9 Hz). MS, *m*/*z* (%): 366 (100) [M$^+$], 221 (25), 220 (28), 203 (32), 188 (25), 187 (36), 134 (80), 133 (34), 121 (37). Found (%): C, 62.56; H, 4.88; N, 15.16. Calc. for $C_{19}H_{18}N_4O_2S$ (%): C, 62.28; H, 4.95; N, 15.29.

For **3c**: yield 15%, mp 236–238 °C. ^{1}H NMR (250 MHz, [$^2H_6$]DMSO) δ: 2.31 (s, 3H, Me), 6.12 (dd, 1H, 3a-H, $^3J_{3a\text{-}H,\ 7a\text{-}H}$ 7.6 Hz, $^3J_{3a\text{-}H,\ NH}$ 2.2 Hz), 6.36 (d, 4H, 7a-H, $^3J_{7a\text{-}H,\ 3a\text{-}H}$ 7.6 Hz), 7.4–7.6 (m, 3H, Ph), 7.7–7.8 (m, 2H, Ph), 8.11 (d, 2H, $C_6H_4NO_2$, *J* 9.2 Hz), 8.26 (d, 2H, $C_6H_4NO_2$, *J* 9.2 Hz), 8.64 (d, 1H, NH, $^3J_{NH,\ 3a\text{-}H}$ 2.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 21.60 (q, Me, *J* 129.2 Hz), 61.95 (ddd, 7a-C, *J* 168.9 Hz, *J* 4.0 Hz, *J* 1.0 Hz), 80.79 (d, 3a-C, *J* 162.1 Hz), 124.20 (dd, 3″-C, $C_6H_4NO_2$, *J* 172.4 Hz, *J* 4.4 Hz), 127.81 (dd, 2″-C, $C_6H_4NO_2$, *J* 168.4 Hz, *J* 7.5 Hz), 128.29 (ddd, 2′-C, Ph, *J* 159.8 Hz, *J* 7.2 Hz), 129.49 (dd, 3′-C, Ph, *J* 161.6 Hz, *J* 7.2 Hz), 132.75 (t, 1′-C, Ph, *J* 7.8 Hz), 132.78 (dt, 4′-C, Ph, *J* 162.9 Hz, *J* 7.4 Hz), 139.09 (t, 1″-C, $C_6H_4NO_2$, *J* 7.7 Hz), 143.71 (m, 5-C), 148.62 (tt, 4′-C, $C_6H_4NO_2$, *J* 9.5 Hz, *J* 3.3 Hz), 167.25 (td, 2-C, J_t 5.4 Hz, J_d 4.9 Hz), 170.97 (d, C=O, *J* 6.4 Hz). MS, *m*/*z* (%): 381 (100) [M$^+$], 339 (27), 236 (45), 218 (32), 203 (22), 202 (50), 149 (42), 121 (55), 104 (34), 103 (54). Found (%): C, 56.72; H, 3.87; N, 18.23. Calc. for $C_{18}H_{15}N_5O_3S$ (%): C, 56.68; H, 3.96; N, 18.36.

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