Regioselective synthesis of novel 4,4'-and 5,5'-bi-(1,2,4-triazole) derivatives

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A regioselective synthesis is reported of a series of polysubstituted 1,2,4-triazoles and 4,4'- and 5,5'-bi-(l,2,4-triazoles) *via* 1,3-dipolar cycloaddition reactions of nitrilimines with some aza- and diaza-butadiene derivatives.

Keywords: 1,2,4-triazoles, 4,4'-bi-(l,2,4-triazoles), 5,5'-bi-(l,2,4-triazoles), nitrilimines, azabutadiene, diazabutadiene

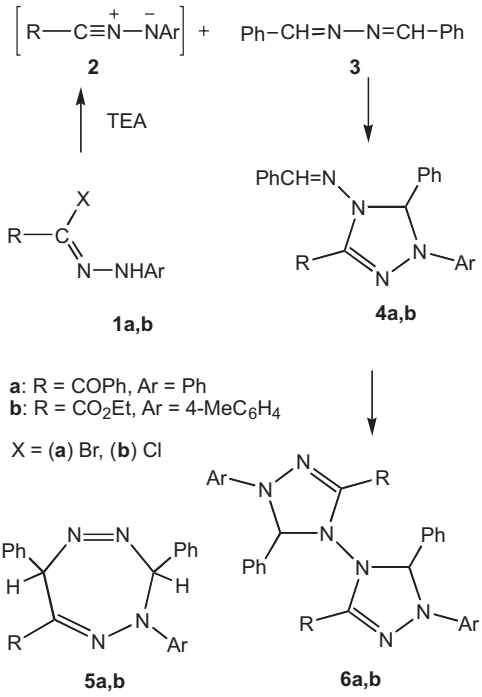
The synthesis of 1,2,4-triazole derivatives has received a considerable attention in view of their diverse pharmacological activities.[1-4] In addition, 3,3'-bis-1,2,4-triazoles have proved to possess bactericidal, fungicidal, and anthelmintic activities.[3] As part of our ongoing research program dealing with the synthesis of a variety of heterocyclic systems for biological evaluation,[5-14] and in continuation of our previous studies concerned with the synthesis of 3,3'-bi-l,2,4-triazole derivatives,[15-17] the present work was undertaken to prepare a series of novel 4,4'- and 5,5'-bi-(1,3,5-trisubstituted-l,2,4-triazole) derivatives *via* 1,3-dipolar cycloaddition reactions of nitrilimines to l,4-diphenyl-2,3-diaza-l,3-butadiene (benzaldehyde azine, **3**) (Scheme 1) and 1,4-di-(4-methylphenyl)-l,4-diaza-l,3-butadiene (**7**) (Scheme 2), respectively, with a view to investigating their potential biological and pharmacological activity. The presence of conjugated carbon–nitrogen double bonds in diazabutadienes **3** and **7** makes these readily accessible compounds potentially useful for the synthesis of 4,4'- and 5,5'-bi-(1,2,4-triazole) derivatives.

Results and discussion

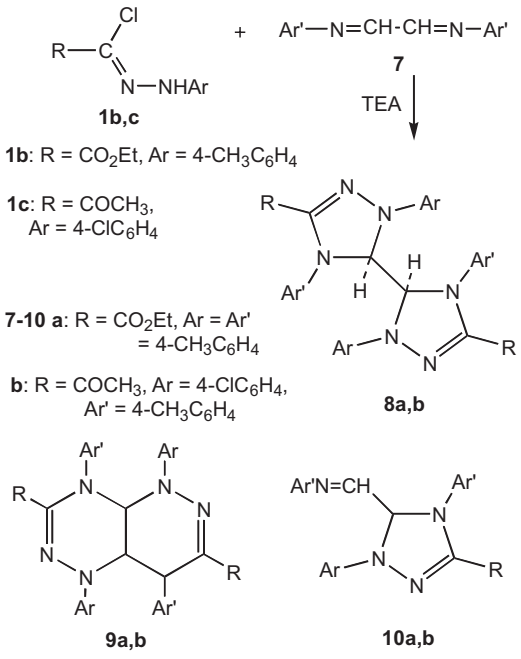
When an equimolar mixture of l,4-diphenyl-2,3-diaza-l,3-butadiene (**3**) and the appropriate hydrazonoyl halide **1** was refluxed in dry benzene in the presence of an equivalent amount of triethylamine, it afforded, in each case, only 1 : 1 cycloadduct. In principle, two possible isomeric structures **4** and **5** can be written for the isolated products (Scheme 1). Among these structures, the 4,5-dihydro-5-phenyl-4-[(phenylmethylene)-amino]-1,3-disubstituted-1*H*-1,2,4-triazole structure **4** was assigned to the isolated cycloadducts on the basis of their spectral data. The ^{1}H NMR spectrum of **4a** revealed, in addition to an aromatic multiplet at δ 7.1–7.8, two singlet signals at δ 6.65 and 8.30 corresponding to the protons at C-5 of the triazoline ring moiety and the azomethine group, respectively. Its mass spectrum showed, in addition to a molecular ion peak at *m/z* 430, a fragment ion of *m/z* 326 corresponding to $[M–PhCH=N]^+$. These findings exclude the possible isomeric seven-membered structure **5** which may arise from [4 + 3] type of cycloaddition.

Treatment of the isolated cycloadducts **4a,b** with an equivalent amount of the corresponding hydrazonoyl halides **1a,b** in benzene, in the presence of triethylamine, afforded the corresponding 4,4',5,5'-tetrahydro-5,5'-diphenyl-1,1',3,3'-tetrasubstituted 4,4'-bi-1*H*-1,2,4-triazole derivatives **6a,b** in good yields similar to analogously reported bitriazole derivatives.[16] Their ^{1}H NMR spectra revealed, in each case, the lack of the characteristic singlet signal at δ 8.3 corresponding to the azomethine proton in **4** and showed a singlet signal in the region δ 6.6–6.9 due to the two protons at C-5 and C-5' of the bi-1,2,4-triazole ring system.

Next, the reaction of the 1,4-diazabutadiene derivative **7** with an equimolar amount of the hydrazonoyl chloride **1b**, under similar experimental conditions, furnished two isolable products. Mass spectrometry and ^{1}H NMR spectra of the isolated products showed that one of them is the starting material **7** and the other is the 1 : 2 cycloadduct **8a** but in a fair yield. (Scheme 2) The latter cycloadduct was obtained



Scheme 1



Scheme 2

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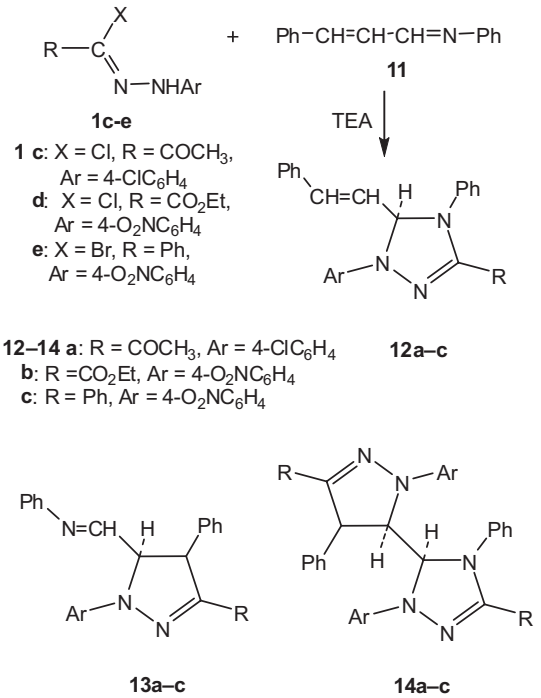
solely by reaction of **7** with the hydrazonoyl chloride **1b** in 1 : 2 molar ratio. This result reflects the higher reactivity of the 1,4-diazabutadiene derivative **7** than its 2,3-isomer **3**. ^{1}H NMR spectrum of **8a** was free of the azomethine proton signal at δ 8.38, shown in the ^{1}H NMR spectrum of **7** and displayed a singlet signal at δ 5.55 integrated for the two chemically equivalent vicinal protons at C-5 and C-5' of bi-triazoline ring system. The molecular ion peak was virtually absent in the mass spectrum of the bi-triazoline derivative **8a**: however, it showed instead an abundant fragment ion peak at *m/z* 322 corresponding to $M^+/2$. This mode of fragmentation excludes the fused bicyclic structure **9a** formed by criss-cross cycloaddition. Similar observations were recorded on treatment of compound **7** with the hydrazonoyl chloride **1c** in 1:2 molar ratio, where the bi-triazoline cycloadduct **8b** was exclusively obtained in a good yield. All attempts to isolate the 1:1 cycloadducts **10a,b** were unsuccessful.

The reaction of nitrilimines **1c,d,e** with 1,4-diphenyl-1-aza-1,3-butadiene (**11**) was also investigated. Thus, it has been found that reaction of hydrazonoyl halides **1c,d,e** with **11** in an equimolar ratio, in benzene and in the presence of equivalent amount of triethylamine, either at room temperature or at mild reflux afforded, in each case, 1 : 1 cycloadducts identified as 4,5-dihydro-1,3,4-trisubstituted-5-styryl-1*H*-1,2,4-triazoles **12a–c** (Scheme 3). The mass spectra of the formed products exhibited in each case a peak corresponding to the molecular ion (M^+). ^{1}H NMR spectrum of **12a**, as an example, was free of the characteristic azomethine N=CH proton signal that was present in the starting cinnamaldehyde anil **11** at δ 8.3 and revealed a doublet at δ 6.09 and a doublet of doublets at δ 6.34 due to olefinic CH=CH protons in addition to a doublet at δ 6.71 due to the triazoline-5-CH proton. This finding excludes the other possible isomeric structures **13** for the reaction products. It is noteworthy that, treatment of compounds **12a–c** with an excess of nitrilimines **2** gave no further reaction and the starting materials **12a–c** were recovered unchanged. Moreover, the reaction of **11** with two equivalents of hydrazonoyl halide **1**, in the presence of triethylamine, afforded the same 1:1 cycloadducts **12a–c** and there was no evidence for the formation of the 4,5-dihydropyrazolyl-1,2,4-triazole derivatives **14**, resulting from the addition of nitrilimine dipoles **2** on the carbon-carbon double bond of the styryl group in **12**.



Scheme 3

Experimental

Melting points were measured with a Gallenkamp apparatus. The IR spectra were recorded of samples in KBr on a Shimadzu FT-IR 8101 PC IR spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Centre of Cairo University. Butadiene derivatives **3,**[18] **7**[19] and **11**[20] and hydrazonoyl halides **1a,**[21] **1b,**[22] **1d,**[23] **1c,**[24] and **1e**[25] were prepared according to literature procedures.

4,5-Dihydro-5-phenyl-4-N-[(phenylmethylene)amino]-1H-1,2,4-triazoles **4a** *and* **4b**

Equimolar quantities of the 1,4-diphenyl-2,3-diaza-1,3-butadiene (**3**) (0.416 g, 2 mmol) and the appropriate hydrazonoyl halide **la,b** (2 mmol) were dissolved in dry benzene (20 ml). To the resulting solution triethylamine (0.2 ml, 2 mmol) was added and the mixture was refluxed for 3 h then left to cool. The solvent was evaporated under reduced pressure and the oily residue was triturated with methanol. The solid product so formed was collected by filtration and recrystallised from the indicated solvent to afford **4a** and **4b,** respectively.

3-Benzoyl-1,5-diphenyl compound (**4a**): Bright orange solid (methanol) (0.75 g, 87%), m.p. 140–141°C. IR: ν_{max} 1650 (C=O), 1600 cm^{-1} (C=N). ^{1}H NMR: δ 6.65 (s, 1H, triazoline-5-CH), 7.1–7.8 (m, 20H, ArH), 8.3 (s, 1H, N=CH); *m/z* 430 (M^+). Found: C, 78.25; H, 4.90; N, 13.17. $C_{28}H_{22}N_4O$ requires C, 78.10; H, 5.15; N, 13.02%.

Ethyl 5-phenyl-1-p-tolyl-3-carboxylate (**4b**): Yellow crystals (petroleum ether/benzene) (0.49 g, 60%), m.p 100–102°C. IR: ν_{max} 1730 (C=O), 1600 cm^{-1} (C=N). MS: *m/z* 412 (M^+), 308 (M^+- PhCH=N), 104 (PhCH=N). Found: C, 73.00; H, 5.84; N, 13.67. $C_{25}H_{24}N_4O_2$ requires C, 72.79; H, 5.87; N, 13.58%.

4,4',5,5'-Tetrahydro-5,5'-diphenyl-1,1',3,3'-tetrasubstituted-[4,4'-bi-1H-1,2,4-triazoles] **6a** *and* **6b.**

Equimolar (2 mmol) quantities of the appropriate 4(*N*-phenylmethyleneamino)-1,2,4-triazole derivative **4a,b** and the corresponding hydrazonoyl halide **1a,b** were dissolved in hot benzene (15 ml). Triethylamine (0.2 ml, 2 mmol) was added and the reaction mixture was refluxed for 3 h, then left to cool. The solvent was distilled off under reduced pressure and the oily residue was triturated with methanol. The solid product was collected by filtration and recrystallised from ethanol to afford **6a** and **6b**, respectively.

3,3'-Dibenzoyl compound **6a:** Orange-red solid (methanol) (1.02 g, 78%) m.p. 173–174°C. IR: ν_{max} 1650 (C=O), 1600 cm^{-1} (C=N). ^{1}H NMR: δ 6.64 (s, 2H), 6.90–8.32 (m, 30H, Ar H). Found: C, 77.10; H, 4.90; N, 12.76. $C_{42}H_{32}N_6O_2$ requires C, 77.28; H, 4.94; N, 12.88%.

Diester **6b:** Yellow crystals (pet. ether/benzene) (0.78 g, 63%), m.p. 110–111°C. IR: ν_{max} 1710 (C=O); 1610 cm^{-1} (C=N). ^{1}H NMR: δ 1.5 (t, 6H), 2.4 (s, 6H) 4.5 (q, 4H), 6.9 (s, 2H, triazole-5-CH), 7.15–7.55 (m. 18H, ArH); *m/z* 308 (M^+/2). Found: C, 69.97; H, 5.68; N, 13.65. $C_{36}H_{36}N_6O_4$ requires C, 70.11; H, 5.88; N, 13.63%.

4,4',5,5'-Tetrahydro-4,4'-di-(4-tolyl-1,1',3,3'-tetrasubstituted-[5,5'-bi-1H-1,2,4-triazoles] **8a** *and* **8b**

Equimolar quantities of the 1,4-di-(*p*-tolyl)-1,4-diaza-l,3-butadiene (**7**) (0.472 g, 2 mmol) and the appropriate hydrazonoyl halide **lb,c** (2 mmol) were dissolved in dry benzene (15 ml). To the resulting solution triethylamine (0.2 ml, 2 mmol) was added. The reaction mixture was refluxed for 3 h and the solvent was removed under reduced pressure. The oily residue was triturated with methanol and the solid product was collected by filtration and crystallised from ethanol.

Diester **8a:** Yellow needles (methanol) (0.54 g, 42%), m.p. 197–198°C. IR: ν_{max} 1730 (C=O), 1600 cm^{-1} (C=N). ^{1}H NMR: δ 1.26 (t, 6H, 2 × ester CH_3) 2.27 (s, 6H), 2.29 (s, 6H), 4.30 (q, 4H, 2 × ester CH_2), 5.55 (s, 2H, bitriazoline-5,5'-CH), 7.04–7.17 (m, 16H, Ar H), *m/z* 322 (M^+/2). Found: C, 70.60; H, 6.10; N, 13.23. $C_{38}H_{40}N_6O_4$ requires C, 70.78; H, 6.25; N, 13.03%.

Diketone **8b:** Pale yellow crystals (methanol) (0.41 g, 33%), m.p. 180–181°C. IR: ν_{max} 1670 (C=O), 1603 cm^{-1} (C=N). ^{1}H NMR: δ 2.30 (s, 6H, *p*-CH_3), 2.43 (s, 6H, CH_3CO) 5.85 (s, 2H,

bitriazoline-5,5'-CH), 6.89–7.23 (m,16H, Ar H). MS: *m/z* 314 (37), 312 (100%) ($M^+/2$). Found: C, 65.34; H, 4.71; N, 13.62; C1, 11.42. $C_{34}H_{30}C1_2N_6O_2$ requires C, 65.27; H, 4.83; N, 13.43; Cl, 11.36%.

4,5-Dihydro-1,3,4-trisubstituted-5-styryl-1H-1,2,4-triazoles **l2a–c**
Equimolar quantities of 1,4-diphenyl-l-aza-l,3-butadiene (**11**) (0.414 g, 2 mmol) and the appropriate hydrazonoyl halide **1c-e** (2 mmol) were dissolved in dry benzene (15 ml). To the resulting solution triethylamine (0.2 ml, 2 mmol) was added, the reaction mixture was refluxed for 3 h then left to cool. The solvent was distilled off under reduced pressure and the residual oil was triturated with methanol. The solid product was collected by filtration and crystallised from the appropriate solvent to afford **l2a–c.**

Ketone **12a:** Bright yellow crystals (ethanol) (0.60 g, 75%), m.p. 160–161°C. IR: ν_{max} 1680 (C=O), 1600 cm^{-1} (C=N). ^1H NMR: δ 2.6 (s, 3H), 6.15 (d, 1 H, *J* = 7.6 Hz), 6.3 (dd, 1 H, *J* = 15.6, 7.8 Hz), 6.75 (d, 1 H, *J* = 15.6 Hz), 7.02–7.4 (m, 14H, Ar' H). MS: *m/z* 401 (M^+). Found: C, 71.82; H, 5.16; N, 10.62; C1, 8.10. $C_{24}H_{20}ClN_3O$ requires C, 71.72; H, 5.02; N, 10.46; Cl, 8.82%.

Ester **12b:** Yellow crystals (ethanol) (0.65 g, 74%), m.p. 134–135°C. IR: ν_{max} 1732 (C=O), 1600 cm^{-1} (C=N). ^1H NMR: δ 1.18 (t, 3H), 4.26 (q, 2H), 6.49 (dd, l H, *J* = 15.4, 8.0 Hz), 6.82 (d, 1 H, *J* = 8.0 Hz), 7.01 (d. 1H, *J* = 15.6 Hz), 7.20-8.19 (m, 14H, Ar'H). MS: *m/z* 442 (M^+). Found: C, 67.69; H, 4.90; N, 12.48. $C_{25}H_{22}N_4O_4$ requires C, 67.86; H, 5.01; N, 12.66%.

Styryltriaryl product **12c:** Pale yellow crystals (ethanol/DMF) (0.64 g, 72%), m.p. 285°C. IR: ν_{max} 1615 cm^{-1} (C=N). ^1H NMR: δ 6.55 (dd, 1H, *J* = 15.6, 7.6 Hz), 6.75 (d, 1 H *J* = 7.6 Hz), 7.0–8.2 (m, 20H, ArH and olefinic CH). MS: *m/z* 446 (M^+). Found: C, 75.42; H, 5.05; N, 12.66. $C_{28}H_{22}N_4O_2$ requires C, 75.32; H, 4.97; N, 12.55%.

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