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Monocyclic 1,2,3-Triazin-4(3*H*)-ones: Synthesis, Structure and Photochemical Behaviour

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Oxidation of the easily available 1-(alkylamino)pyrazolones allows the preparation of the title compounds, which are a new class of heterocycles, in good yields. The structure of these compounds is assigned on the basis of HR mass spectroscopy and sodium borohydride reduction to (*Z*,*E*)-2-methyl-3-phenyl-*N*-(1-phenylethyl)acrylamide. Ring contraction/rearrangement to 2-alkyl-*2H*-1,2,3-triazole is observed under UV irradiation. A possible mechanistic rationalisation of the observed processes is proposed.

Introduction

Ring-condensed 1,2,3-triazin-4-ones are a class of heterocyclic derivatives that have been widely investigated for their biological and chemical properties, and compounds with sedative, diuretic, anaesthetic, antiarthritic and antitumoural activities have been reported.[1] Suitably substituted benzo-1,2,3-triazin-4-ones have been described as potent inhibitors of matrix metalloproteinases,[2] recombinant human histone deacetylases[3] and as ligands of 5-HT_{1A} serotonin receptors.[4] In addition, they are used as an activating moiety in coupling agents for the preparation of peptides and modified nucleosides.[5] However, in spite of a potential analogous interest, the corresponding monocyclic derivatives are completely unknown: to the best of our knowledge, only the preparation of some mesoionic compounds belonging to the 1,2,3-triazin-4,6-dione has been reported.[6]

In this paper we describe a facile access to the title compounds and some aspects of their reactivity, with the purpose of structural assignment and gaining information about heterocyclic ring photochemical behaviour.

Results and Discussion

Benzo-fused 1,2,3-triazine derivatives and several monocyclic aromatic 1,2,3-triazines are usually prepared by oxidative rearrangement of a suitably substituted *N*-aminopyrazole.[7] As a consequence, we decided to extend this strategy to the synthesis of monocyclic 1,2,3-triazin-4-ones by using aminopyrazolones, a class of heterocyclic derivatives which some years ago we considered from a synthetic and chemical reactivity point of view, as substrates.[8]

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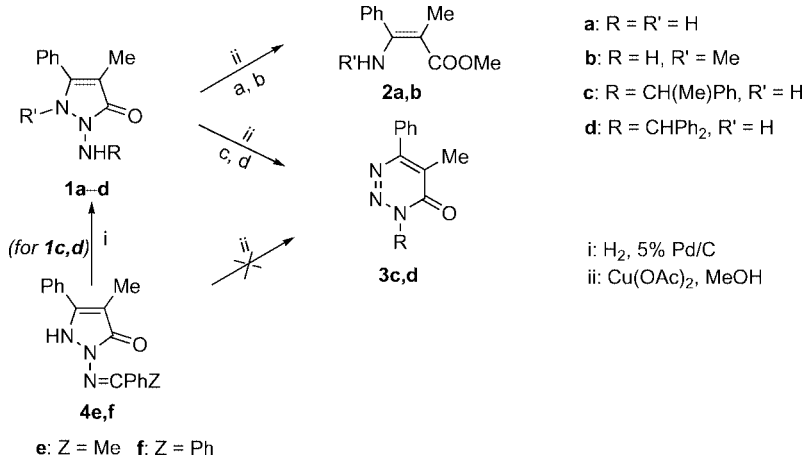
However, when aminopyrazolones **1a**,**b** were treated with copper acetate in methanol, an unexpected ring fragmentation/solvent addition occurred to give the enamino esters **2a**,**b** (Scheme 1).

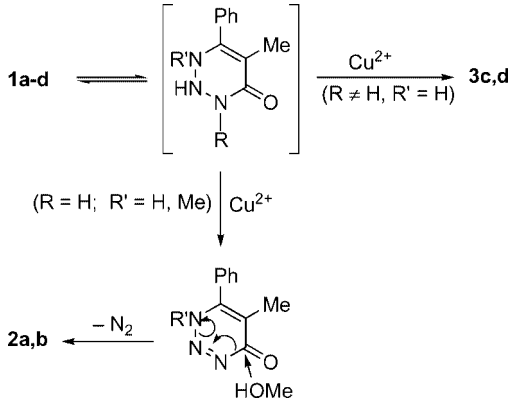
On the other hand, treatment of the *N*-(alkylamino)pyrazolones **1c**,**d** with the same reagent gave the 1,2,3-triazinones **3c**,**d** in good yields. A slower but identical reaction was observed when **1c**,**d** was treated with oxygen in the presence of a mild base such as sodium hydrogen carbonate. It should be noted that the corresponding imine **4c**, which is a potential intermediate for the transformation of **1c** into **3c**, is completely unaltered under the above reaction conditions.

A possible rationalisation of the oxidative behaviour of differently substituted 1-aminopyrazolones is reported in Scheme 2. Ring enlargement/oxidation of the starting material affords, when R is not H, a stable and isolable 3-alkyl-1,2,3-triazin-4(3*H*)-one (compounds **3c**,**d**). Otherwise, when R = R′ = H or R = H and R′ = Me, an unstable 1,2,3-triazin-4(1*H*)-one is formed, which, after solvent attack on the activated carbonyl group followed by N_2 loss, finally gives the enamino esters **2a**,**b**.

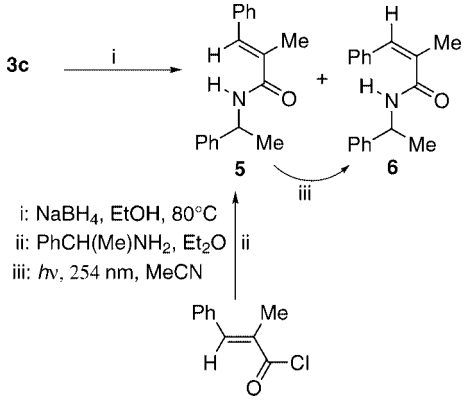
As far as the structure of the new compounds **3c**,**d** is concerned, the presence of the 1,2,3-triazin-4-one system was supported by analytical and spectroscopic data (see Exp. Sect.). In particular, the N=N–N–R sequence was deduced by mass spectroscopy, which shows the loss of 28 amu from the molecular ion: HRMS analysis allowed us to assign this process to the elimination of a molecule of N_2. Furthermore, the substituent positions on the 1,2,3-triazinone system followed from the reductive transformation of **3c** into a mixture of the (*E*,*Z*)-amides **5** and **6** (Scheme 3). To confirm this assignment, compound **5** was independently prepared by treatment of (*E*)-2-methyl-3-phenylacryloyl chloride with 1-phenylethylamine; photochemical isomerisation of compound **5** also allowed us to obtain the (*Z*)-isomer **6**.



Scheme 1.

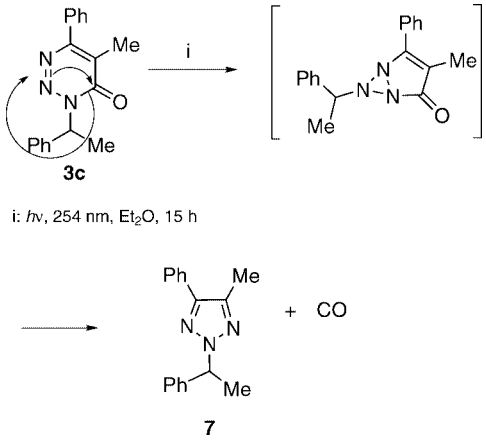


Scheme 2.



Scheme 3.

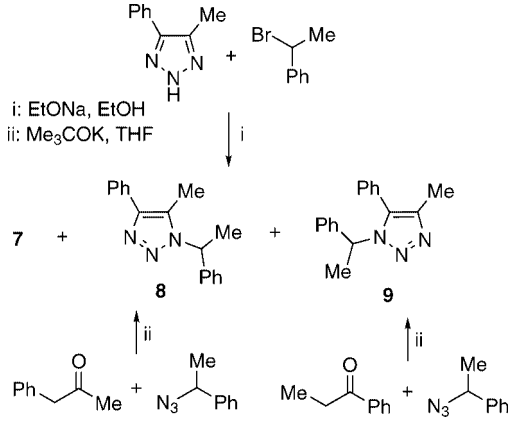
Following our continuing interest in the synthetic and mechanistic aspects of heterocycles' photochemistry,[9] and owing to the novelty of this class of 1,2,3-triazinone derivatives, we also studied their photoreactivity with the aim of investigating the potential synthetic value of this process. UV irradiation gave a slow transformation of the triazinone **3c** into a product of molecular formula $C_{17}H_{17}N_3$, deriving from the loss of a CO moiety, which can be presumably identified as an *N*-substituted 1,2,3-triazole derivative. Absence of an [M – 28] ([M – N_2]) fragment in the HR mass spectrum of this compound and lack of an NOE to the phenyl protons of the N-substituent upon irradiation of the methyl signal at δ = 2.47 ppm suggests the unexpected photochemical formation of compound **7**, as shown in Scheme 4.



Scheme 4.

In order to confirm this structural assignment, we decided to independently prepare all the *N*-(1-phenylethyl)-phenylmethyl-substituted 1,2,3-triazoles. As shown in Scheme 5, compounds **8** and **9** were obtained by reaction of (1-azidoethyl)benzene with methyl benzyl ketone or propiophenone, respectively, following a procedure previously reported for the selective access to 1-substituted triazoles.[10] Compound **7** was prepared as the main product by alkylation of the corresponding 4-methyl-5-phenyl-1,2,3-triazole with 1-chloro-1-phenylethane in the presence of a base. Minor amounts of the isomers **8** and **9** were also obtained. In this way it was possible to unequivocally assign the structure **7** to the photochemical product obtained from **3c**. It should be noted that the triazoles **8** and **9** are stable under the same irradiation conditions. As a consequence, the photochemical path from **3c** to **7** requires, after CO elimination, a molecular rearrangement of the heterocyclic system. A possible mechanistic scheme for the formation of **7** is shown in Scheme 4. In analogy with the well known oxa-di-π-

methane photorearrangement of substituted 2,4-cyclohexadienones[11a,b] and of the very similar behaviour of the corresponding aza-analogue pyridones,[11c] the excited 1,2,3-triazin-4(3*H*)-one system affords an unstable 1,5,6-triazabicyclo[3.1.0]hex-3-en-2-one, which finally gives the stable, aromatic triazole **7** by loss of carbon monoxide.



Scheme 5.

Conclusions

Oxidation of *N*-(alkylamino)pyrazolones is a good and general strategy for the preparation of monocyclic 1,2,3-triazin-4-ones. The photochemical behaviour of these compounds (loss of carbon monoxide and rearrangement to a 2-alkyl-2*H*-1,2,3-triazole) is completely different from benzo-condensed 1,2,3-triazinones, for which N_2 elimination and benzoazetidinone formation was previously observed.[12]

Experimental Section

General: Melting points were determined on a Kofler hot stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ on a Bruker AC 200 spectrometer at 200.13 and 50.33 MHz, respectively. Chemical shifts are reported in ppm from internal TMS. All chemicals were of reagent grade and were used without purification. Photochemical reactions were carried out in a quartz apparatus with a low-pressure mercury immersion lamp (12 W); nitrogen was bubbled constantly through the irradiated solution. The EI and FAB mass spectra were recorded with a VG 70 250S instrument in low resolution mode (1000 M/ΔM, 10% valley) or high resolution mode (EI-HRMS, 10,000 M/ΔM, 10% valley); electrospray ionisation spectra (ESI MS) were recorded with a LCQ-DECA Thermo Finnigan instrument. Analytical or preparative chromatography was performed on precoated 4×6.7 or 20×20 silica gel 60 F254 plates, respectively. Column chromatography was carried out on silica gel (0.063–0.2 mm). Compounds **1a**,**b** were prepared as described previously.[8c]

4-Methyl-5-phenyl-2-(1-phenylethylamino)-1,2-dihydropyrazol-3-one (1c): 5% Pd/C (0.125 g) was added to a solution of 4-methyl-5-phenyl-2-(1-phenylethylideneamino)-1,2-dihydropyrazol-3-one[8a] (0.40 g, 1.37 mmol) in methanol (20 mL) and the mixture was hydrogenated (room temp.) overnight at 30 psi. After removal of the catalyst by filtration, the solution was evaporated in vacuo and the residue was chromatographed with chloroform to give compound **1c** (0.35 g, 87% yield), which was crystallised from cyclohexane, m.p. 127–128 °C. ^{1}H NMR:[13] δ = 1.14* (d, J = 8.0 Hz, 1.7 H, 4-Me), 1.39, 1.45*,# (d, J = 8.0 Hz, 3 H, 2-CH*Me*), 2.01# (s, 1.3 H, 4-Me), 3.42* (q, J = 8.0 Hz, 0.6 H, 4-CH), 4.12 (m, 1.4 H, NH/OH), 4.63 (m, 1 H, 2-*CH*Me), 7.35–7.61 (m, 10 H, aryl) ppm. ESI MS: *m*/*z* (%) 609 (54) $[2M + Na]^+$, 316 (100) $[M + Na]^+$, 294 (14) $[MH]^+$. $C_{18}H_{19}N_3O$ (293.15): calcd. C 73.72, H 6.48, N 14.33; found C 73.90, H 6.75, N 14.10.

2-(Benzhydrylamino)-4-methyl-5-phenyl-1,2-dihydropyrazol-3-one (1d): A mixture of benzophenone (1.45 g, 8.0 mmol) and **1a** (1 g, 5.3 mmol) was heated at 90 °C for 3 h. After cooling to room temp., the reaction mixture was sublimed at 100 °C and 0.5 Torr for approximately 2 h to remove the excess benzophenone. The solid residue was washed with diethyl ether and filtered to give 2-(diphenylmethyleneamino)-4-methyl-5-phenyl-1,2-dihydropyrazol-3-one (**4d**; 1.08 g, 58% yield), which was recrystallised from ligroin, m.p. 178–181 °C. ^{1}H NMR:[13] δ = 1.41* (d, J = 8.0 Hz, 1.8 H, 4-CH*Me*), 2.07# (s, 1.2 H, 4-Me), 3.50# (q, J = 7.8 Hz, 0.6 H, 4-CH), 7.33–7.80 (m, 15 H, aryl) ppm. $C_{23}H_{19}N_3O$ (353.15): calcd. C 78.16, H 5.42, N 11.89; found C 78.01, H 5.58, N 11.63.Catalytic hydrogenation of **4d**, as described above for the synthesis of **1c**, gave compound **1d** (65% yield), m.p. 67–70 °C from benzene. ^{1}H NMR:[13] δ = 1.15* (d, J = 7.8 Hz, 1.8 H, Me), 1.97# (s, 1.2 H, 4-Me), 4.92 (m, 1.4 H, NH/OH), 3.37* (q, J = 7.8 Hz, 0.6 H, 4-CH), 5.20# (s, 0.4 H, 2-*CH*Ph), 5.76* (s, 0.6 H, 2-*CH*Ph), 7.02–8.20 (m, 15 H, aryl) ppm. ESI MS: *m*/*z* (%) 733 (23) $[2M + Na]^+$, 378 (30) $[M + Na]^+$, 356 (19) $[MH]^+$. $C_{23}H_{21}N_3O$ (355.17): calcd. C 77.72, H 5.96, N 11.82; found C 77.65, H 5.56, N 12.10.

General Procedure for the Oxidation of Compounds 1a–d: Anhydrous copper acetate (3.5 mmol) was added to a solution of compounds **1a**–**d** (3.5 mmol) in methanol (75 mL) and the mixture stirred at reflux until the starting material disappeared (TLC). After filtration of the insoluble inorganic solid, the solvent was removed in vacuo and the residue column chromatographed with chloroform to give compounds **2a**,**b** or **3c**,**d**, respectively.

Methyl 3-Amino-2-methyl-3-phenylacrylate (2a): The residue obtained from compound **1a** was identified as the aminoacrylate **2a** (0.52 g, 78% yield) by comparison with an authentic sample.[14]

Methyl 2-Methyl-3-(methylamino)-3-phenylacrylate (2b): The residue obtained from compound **1b** was identified as the methylaminolacrylate **2b** (0.54 g, 75% yield) by comparison with an authentic sample.[15]

5-Methyl-6-phenyl-3-(1-phenylethyl)-1,2,3-triazin-4(3*H*)-one (3c): The residue obtained from compound **1c** was purified by sublimation in vacuo to give the 1,2,3-triazinone **3c** as white needles (0.77 g, 75.6% yield), m.p. 88–90 °C. ^{1}H NMR: δ = 1.99 (d, J = 7.8 Hz, 3 H, 3-CH*Me*), 2.22 (s, 3 H, 5-Me), 6.37 (q, J = 7.8 Hz, 1 H, 3-*CH*Me), 7.32–7.55 (m, 10 H, aryl) ppm. ^{13}C NMR: δ = 12.34, 20.11, 57.03, 125.15, 127.49, 128.07, 128.35, 128.56, 129.20, 129.62, 134.45, 139.82, 153.96, 157.34 ppm. FAB MS: *m*/*z* (%) 292 (100) $[MH]^+$, 264 (32), 220 (8), 188 (63), 160 (32), 105 (94). EI HRMS: *m*/*z* (%) 291.1371 (0.5) $[M]^+$, 263.1427 (26) $[M - N_2]^+$. $C_{18}H_{17}N_3O$ (291.14): calcd. C 74.20, H 5.88, N 14.42; found C 73.90, H 5.60, N 14.71.

3-Benzhydryl-5-methyl-6-phenyl-1,2,3-triazin-4(3*H*)-one (3d): The residue obtained from compound **1d** was purified by crystallisation from light petroleum to give compound **3d** as a white powder (0.75 g, 60.4% yield), m.p. 127–129 °C. ^{1}H NMR: δ = 2.29 (s, 3 H, 5-Me), 7.36–7.63 (m, 11 H, aryl and 3-CH) ppm. ^{13}C NMR: δ = 13.52, 61.11, 121.61, 123.30, 123.79, 124.22, 124.60, 124.93, 125.26,

125.71, 126.13, 126.59, 127.33, 130.75, 134.63, 150.28, 154.10 ppm. ESI MS: *m/z* (%) 729 $[2M + Na]^+$, 392 $[M + K]^+$, 376 $[M + Na]^+$. EI HRMS: *m/z* (%) 353.1526 (0.7) $[M]^+$, 325.1467 (23) $[M - N_2]^+$. $C_{23}H_{19}N_3O$ (353.15): calcd. C 78.17, H 5.42, N 11.89; found C 78.26, H 5.49, N 11.82.

(*E*)-2-Methyl-3-phenyl-*N*-(1-phenylethyl)acrylamide (5): A solution of 1-phenylethylamine (0.4 g, 2 mmol) in diethyl ether (25 mL) was slowly added to a solution of (*E*)-2-methyl-3-phenylacryloyl chloride (0.3 g) in diethyl ether (10 mL). After 1 h the mixture was washed with 0.1 N HCl solution and then with water. The ethereal solution was separated, dried with Na_2SO_4 and evaporated to afford the (*E*)-amide **5** (0.35 g, 80%), which was crystallised from ethanol/water. M.p. 96–97 °C. ^{1}H NMR: δ = 1.60 (d, *J* = 6.9 Hz, 3 H, NHCH*Me*), 2.12 (d, *J* = 1.4 Hz, 3 H, 2-Me), 5.28 (quint, *J* = 6.9, 1 H, NH*CH*Me), 6.27 (d, *J* = 6.9 Hz, 1 H, NH), 7.26–7.50 (m, 11 H, aryl and 3-CH) ppm. $C_{18}H_{19}NO$ (265.15): calcd. C 81.47, H 7.22, N 5.28; found C 81.62, H 7.05, N 5.11.

(*Z*)-2-Methyl-3-phenyl-*N*-(1-phenylethyl)acrylamide (6): A solution of the amide **5** (0.1 g) in acetonitrile (100 mL) was irradiated, at 254 nm, with a low-pressure mercury lamp for 2.5 h. TLC and the NMR spectrum of the reaction mixture indicated the formation of a photostationary 1:1 mixture of (*E*) and (*Z*) isomers. The two products were separated by preparative layer chromatography, eluting with cyclohexane/ethyl acetate (2:1) to give (in order of elution) the unreacted amide **5** (0.04 g) and the isomeric amide **6** (0.040 g) as an oil. ^{1}H NMR: δ = 1.30 (d, *J* = 7.0 Hz, 3 H, NHCH*Me*), 2.10 (d, *J* = 1.6 Hz, 3 H, 2-Me), 5.10 (quint, *J* = 7.0 Hz, 1 H, NH*CH*Me), 5.45 (d, *J* = 7.0 Hz, 1 H, NH), 7.31–7.50 (m, 11 H, aryl and 3-CH) ppm. $C_{18}H_{19}NO$ (265.15): calcd. C 81.47, H 7.22, N 5.28; found C 81.25, H 7.13, N 5.42.

(*E*,*Z*)-2-Methyl-3-phenyl-*N*-(1-phenylethyl)acrylamide (5 and 6): Sodium borohydride (0.065 g, 1.7 mmol) was added to a solution of the triazinone **3c** (0.05 g, 0.17 mmol) in ethanol (15 mL). The mixture was heated for 5 h at 80 °C in an ultrasound bath and then evaporated, washed with acid water (10 mL), extracted with diethyl ether and dried over Na_2SO_4. The ethereal solution was evaporated to give a mixture of the two isomeric amides **5** and **6** in a 4:1 ratio, as determined by NMR spectroscopy.

4-Methyl-5-phenyl-2-(1-phenylethyl)-2*H*-1,2,3-triazole (7): A solution of triazinone **3c** (0.07 g, 0.24 mmol) in anhydrous diethyl ether (50 mL) was irradiated with a low-pressure lamp for 15 h. The solution was evaporated and the residue chromatographed on a preparative plate, eluting with petroleum ether/diethyl ether (6:1) to give starting material **3c** (0.03 g) as a slower running band and compound **7** (0.015 g, 42% yield, based on the unreacted starting material). M.p. 127–128 °C. ^{1}H NMR: δ = 1.99 (d, *J* = 7.2 Hz, 3 H, 2-CH*Me*), 2.47 (s, 3 H, 4-Me), 5.79 (q, *J* = 7.2 Hz, 1 H, 2-CH), 7.27–7.47, 7.67–7.72 (m, 10 H, aryl) ppm. ^{13}C NMR: δ = 11.78, 21.23, 64.11, 126.67, 127.20, 128.05, 128.14, 129.00, 131.58, 140.70, 141.24, 144.60 ppm. EI MS: *m/z* (%) 263 (100) $[M]^+$, 248 (17). EI HRMS: *m/z* (%) 263.1422 (32) $[M]^+$, 248.1189 (12) $[M - Me]^+$. $C_{17}H_{17}N_3$ (263.14): calcd. C 77.54, H 6.51, N 15.96; found C 77.85, H 6.73, N 15,82.

The same compound (identical TLC and NMR spectrum; 1.30 g, 80% yield) was obtained by refluxing 4-methyl-5-phenyl-1,2,3-triazole[16] (1 g, 6.2 mmol) with 1-bromo-1-phenylethane (0.85 mL, 6.2 mmol) in anhydrous ethanol (10 mL) containing sodium (0.14 g, 6.2 mmol). NMR analysis of the reaction mixture showed the formation of minor amounts (<10%) of triazoles **8** and **9**.

5-Methyl-4-phenyl-1-(1-phenylethyl)-1*H*-1,2,3-triazole (8): (1-Azidoethyl)benzene[17] (0.27 mL, 1.8 mmol) and methyl benzyl ketone (0.27 mL, 2 mmol). were added to a 1 M solution of potassium *tert*-butoxide in THF (2 mL). The reaction mixture turned red immediately and was stirred at room temperature for 2 h. It was then poured into ice/water to give an oil, which was extracted with diethyl ether. The ethereal solution was dried over anhydrous magnesium sulfate and then evaporated to give compound **8** (0.15 g, 32% yield; m.p. 103–105 °C) after crystallisation from ethyl acetate/light petroleum. ^{1}H NMR: δ = 2.07 (d, *J* = 7.1 Hz, 3 H, 1-CH*Me*), 2.25 (s, 3 H, 5-Me), 5.57 (q, 1 = H, *J* = 7.1 Hz, 1-CH), 7.18–7.45, 7.65–7.68 (m, 10 H, aryl) ppm. ^{13}C NMR: δ = 9.11, 21.82, 58.66, 125.95, 127.17, 127.45, 127.94, 128.49, 128.86, 128.94, 131.61, 140.62, 144.86 ppm. EI MS: *m/z* (%) 263 (25) $[M]^+$, 235 (3), 220 (9). $C_{17}H_{17}N_3$ (263.14): calcd. C 77.54, H 6.51, N 15.96; found C 77.63, H 6.65, N 16.03.

4-Methyl-5-phenyl-1-(1-phenylethyl)-1*H*-1,2,3-triazole (9): Operating as above, a red solution was obtained from a 1 M solution of potassium *tert*-butoxide in THF (2 mL), (1-azidoethyl)benzene[17] (0.27 mL, 2 mmol) and propiophenone (0.27 mL, 2 mmol), and heated at 65 °C for 1 h in a closed tube. Water was then added to the ice-cooled reaction mixture and this was extracted with diethyl ether. The extracts were dried over anhydrous magnesium sulfate and then evaporated to give the triazole **9** (0.30 g, 74% yield) as an oil, which was purified by distillation at 60 °C and 0.05 Torr. ^{1}H NMR: δ = 1.95 (d, *J* = 3.0 Hz, 3 H, 1-CH*Me*), 2.24 (s, 3 H, 4-Me), 5.41 (q, *J* = 3.0 Hz, 1 H, 1-CH), 7.03–7.13, 7.21–7.26, 7.36–7.41 (m, 10 H, aryl) ppm. ^{13}C NMR: δ = 10.47, 22.39, 58.44, 126.20, 127.75, 128.63, 128.75, 128.95, 129.73, 132.94, 133.66, 134.38, 141.26, 141.39 ppm. EI MS: *m/z* (%) 263 (24) $[M]^+$, 248 (5), 235 (13). $C_{17}H_{17}N_3$ (263.14): calcd. C 77.54, H 6.51, N 15.96; found C 77.68, H 6.42, N 15.75.

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