SHORT PAPER

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A facile synthesis of 2-methyl-1,2,3-triazoles†

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Reaction of α-bromoacetophenone bearing various substituents on the benzene rings with methylhydrazine in refluxing acetic acid afforded 2-methyl-4-phenyl-1,2,3-triazoles. The relation between the substituents and the yields is briefly discussed.

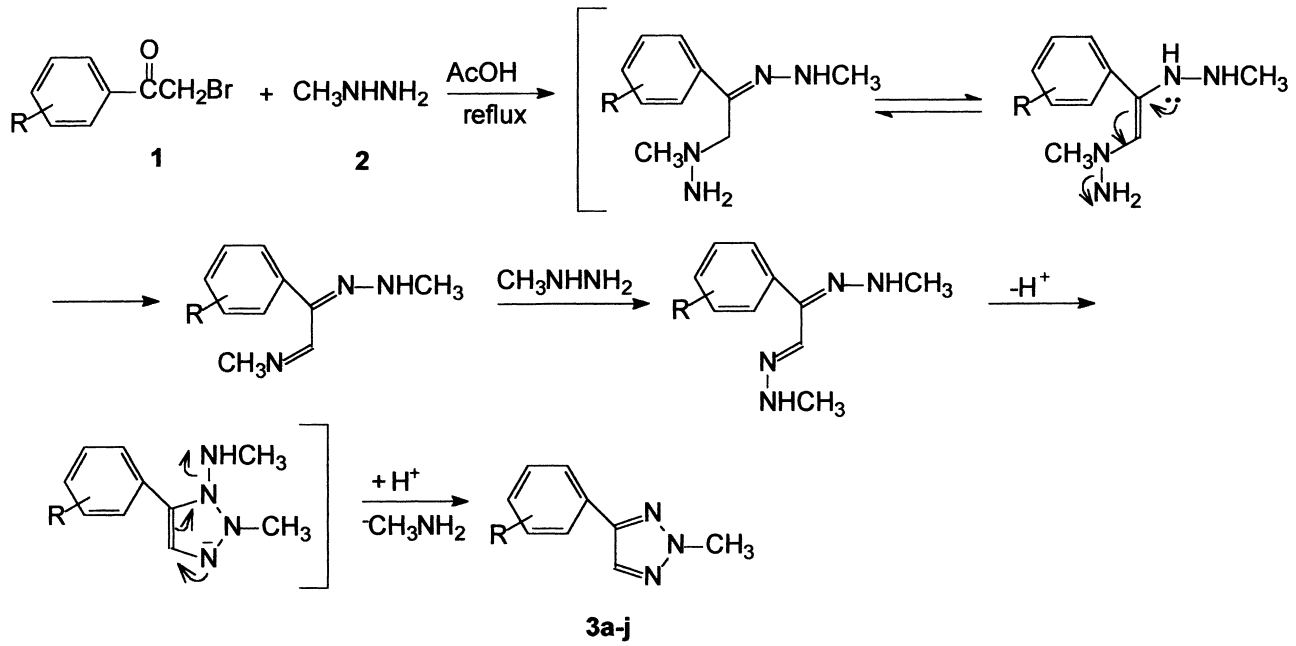
Keywords: 2-methyl-1,2,3-triazoles, methylhydrazones, phenacyl bromides

The 1,2,3-triazole moiety is a very interesting component in terms of biological activity. Indeed, the 1,2,3-triazole moiety is present in a number of drugs such as the human β_3-adrenergic receptor agonist[1], inhibitor of HIV-1 replication[2] or potassium channel activator[3-6], *etc*. The general method for the synthesis of 1,2,3-triazole is the 1,3-dipolar cycloaddition of various azides (or salts thereof) with acetylenes,[7,8] activated methylene compounds,[3] or nitriles.[9] In particular, the intramolecular condensation of bisarylhydrazones has been a method of choice for the synthesis of 2,4-diaryl-1,2,3-triazoles[10-12]. In this paper we report a facile method to obtain a series of 2-methyl-1,2,3-triazoles (**3**) by cyclisation of α-bromoacetophenone with methylhydrazine. The method is more satisfactory in terms of availability of starting materials and one-pot operation than those previously reported.

In the course of our studies on the synthesis of 2-arylimidazo[2,1-*a*]isoquinolines, based on the cyclisation of phenacylisoquinolinium bromide with ammonium acetate in the presence of acetic acid,[13] the ammonium acetate was substituted by methylhydrazine. Unexpectedly, 2-methyl-4-phenyl-1,2,3-triazole (**3a**) was obtained. This suggested that the reaction process could be analogous to an earlier report,[10] and therefore we investigated α-bromoacetophenone as the starting material in reaction with methylhydrazine. The same product was afforded in 59% yield. In order to evaluate the scope of this reaction, various α-bromoacetophenones bearing substituents on the benzene ring were prepared to react with methylhydrazine. The corresponding 2-methyl-4-phenyl-1,2,3-triazoles (**3a–j**) were obtained in moderate to high yields (Table 1). It was also observed that the benzene ring substituents have a considerable influence on the yields: electron-donating substituents lead to higher yields, while electron withdrawing ones result in lower yields. A possible mechanism is proposed here (Scheme 1).

It is noteworthy that, when α-bromoacetophenone was treated with phenylhydrazine, the expected product, 2,4-diphenyl-1,2,3-triazole, was not formed except in the presence of cupric ion. More detailed work on these reactions is in progress in our laboratory.

In summary: we have developed a mild and facile route to 2-methyl-4-phenyl-1,2,3- triazoles. Electron-donating substituents on benzene ring of α-bromoacetophenones lead to higher yields than electron-withdrawing ones.



Scheme 1

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Analytical and spectroscopic data for compounds **3a–j**

No.	R	Yield /%	Mol. formula	m.p./ °C	Calc. (Found) % C	H	N	^{1}H NMR ($CDCl_3$) /δ	IR(KBr) /ν(cm^{-1})
3a	H	59	$C_9H_9N_3$	56	67.91 (68.12)	5.70 (5.65)	26.40 (26.60)	4.23 (s,3H), 7.35 (m,1H), 7.42 (t,2H), 7.77(m,2H), 7.81 (s,1H)	3035, 1476, 1457, 1385, 764, 691
3b	4-Cl	47	$C_9H_8ClN_3$	96-98	55.83 (55.69)	4.16 (4.01)	21.70 (21.4)	4.23 (s,3H), 7.39 (m,2H), 7.70 (m,2H), 7.79(s,1H)	1471, 1377, 829
3c	4-Br	41	$C_9H_8BrN_3$	120-122	45.40 (45.16)	3.39 (3.43)	17.65 (17.4)	4.23 (s,3H), 7.55 (m,2H), 7.64 (m,2H), 7.80 (s,1H)	1473, 1379, 832
3d	3,4-Cl_2	21	$C_9H_7Cl_2N_3$	106-108	47.39 (47.06)	3.10 (3.07)	18.42 (18.68)	4.24 (s,3H), 7.49 (d,1H), 7.59 (m,1H), 7.80 (s,1H), 7.87 (d,1H)	1604, 1564, 1463, 1380, 876, 819
3e	2,4-F_2	6	$C_9H_7F_2N_3$	36-38	55.38 (55.21)	3.62 (3.65)	21.53 (21.61)	4.25 (s,3H), 6.94 (m,2H), 7.93 (m,2H)	1598, 1446, 1383, 860, 831
3f	4-NO_2	11	$C_9H_8N_4O_2$	118-120 (dec.)	52.94 (52.82)	3.95 (4.07)	27.44 (27.26)	4.28 (s,3H), 7.95 (m,3H), 8.29 (m,2H)	1603, 1511, 855
3g	3-Cl-4-CH_3	37	$C_{10}H_{10}ClN_3$	38-40	57.84 (57.67)	4.85 (4.59)	20.23 (20.38)	2.41 (d,3H), 4.23 (s,3H), 7.38 (d,1H), 7.53 (m,1H), 7.65 (d,1H), 7.78 (s,1H)	1613, 1472, 1384, 880, 822
3h	4-CH_3	56	$C_{10}H_{11}N_3$	64-66	69.34 (69.01)	6.40 (6.17)	24.26 (24.04)	2.37 (s,3H), 4.21 (3H), 7.22 (d,2H), 7.65 (d,2H), 7.77 (s,1H)	3035, 1485, 1385, 821
3i	4-CH_3O	73	$C_{10}H_{11}N_3O$	104-106	63.48 (63.34)	5.86 (5.99)	22.21 (21.98)	3.84 (s,3H), 4.21 (s,3H), 6.96 (m,2H), 7.69 (m,2H), 7.74 (s,1H)	1613, 1578, 1483, 1383, 837
3j	4-OH	81	$C_9H_9N_3O$	126-128	61.70 (61.52)	5.18 (5.23)	23.99 (23.85)	4.22 (s,3H), 6.89 (m,2H), 7.63 (m,2H), 7.75 (s,1H)	3195, 1617, 1591, 1492, 1452, 843

Experimental

Melting points were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-400 MHz spectrometer with $SiMe_4$ as the internal standard. IR spectra were recorded on a Bruck Vector 200 spectrophotometer and microanalyses were performed on a MOD-1106 elemental analyzer.

General procedure

Methylhydrazine (1.7 ml, 30 mmol) was added slowly to the solution of α-bromoacetophenone (1.2 g, 6 mmol) in acetic acid (2 ml). The mixture was heated to reflux using an oil bath for about 3 hours. After cooling to room temperature the reaction mixture was neutralised with 20% NaOH solution and then extracted twice with chloroform.The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate : petroleum ether (1 : 15) as eluant to afford **3a** (59 % yield) as a white solid, m.p.: 56 °C (Lit.[9] 58 °C).

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