An Approach to 1-Aryl-1,2,4-triazoles

B.I. Buzykin,* Z.A. Bredikhina
A.E. Arbuzov Institute of Organic and Physical Chemistry, 420083, Kazan, Russia

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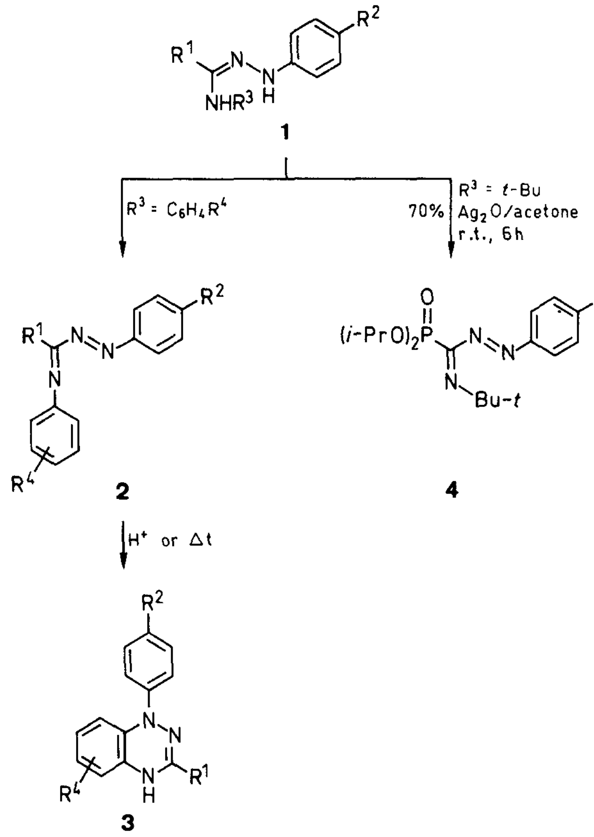
A series of different 1,3,5-trisubstituted 1,2,4-triazoles **9** have been readily prepared by simple oxidation of corresponding *N*-alkylamide arylhydrazones (amidrazones) **5** with hydrogen peroxide or potassium permanganate.

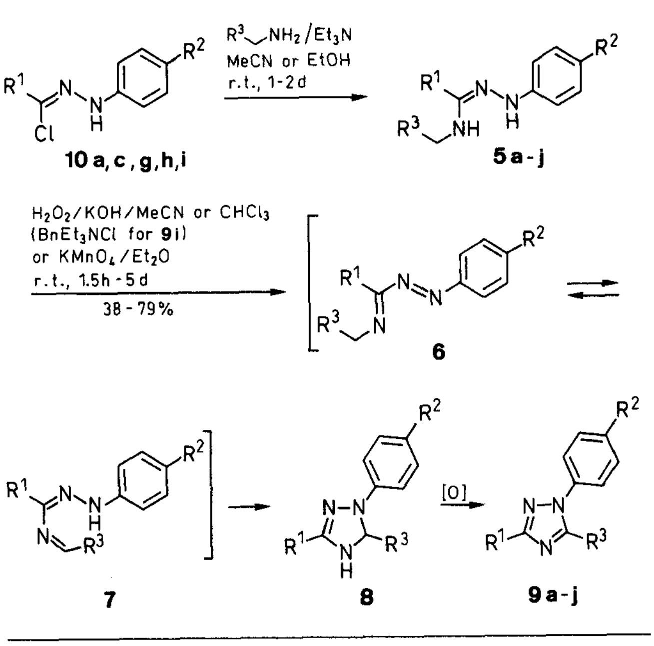
N^2,N^3-Diarylamidrazones **1** are known to undergo oxidation rather readily producing *N*-[1-(arylazo)alkylidene]arylamines **2**.[1,2] Imines **2** are unstable compounds and are rapidly converted into substituted 1,4-dihydro-1,2,4-benzotriazines **3**.[1-3] Newly synthesized *N*-[(4-nitrophenylazo)(diisopropoxyphosphoryl)methylene *tert*-butylamine (**4**) with a tertiary alkyl group at N^3-atom, proved to be more stable (Scheme 1).

We did not succeed in isolating (arylazo)imines **6** with a N^3-methylene group. 1-Aryl-1,2,4-triazoles **9a–i** are formed by oxidation of *N*-alkylamide arylhydrazones **5a–j** with different R^1 and R^3 groups using hydrogen peroxide (H_2O_2), potassium permanganate ($KMnO_4$), or silver(I) oxide (Ag_2O) as oxidizing agents. Transformation of amidrazones **5a–j** into triazoles **9a–j** may proceed through the initial formation not only of azoimines **6**, as well as through their tautomerization into the *N*-alkylideneamide arylhydrazones **7**. Besides the **6** $\rightleftharpoons$ **7** tautomerization they can undergo cyclization into 4,5-dihydro-1,2,4-triazoles **8**, which in turn are oxidized to triazoles **9a–j** (Table). It is a well known fact that attempts to obtain *N*-alkylideneamide arylhydrazones of type **7** and dihydrotriazoles of type **8** lead to the isolation of derivatives of 1,2,4-triazoles.[4,5]

Chromatographic and spectrophotometric control of the oxidation of amidrazone **5j** by $KMnO_4$ in a diethyl ether water two-phase system made it possible to detect an intermediate product besides the initial product **5j** and



Scheme 1

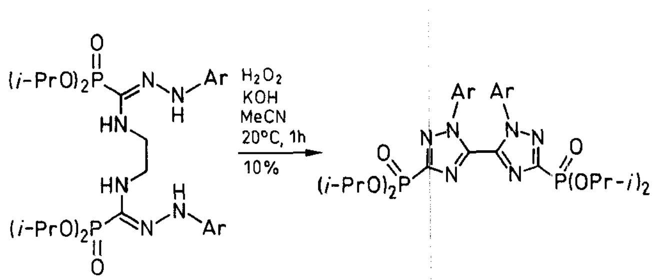


5–10	R^1	R^2	R^3
a	Ph	4-NO_2	H
b	Ph	4-NO_2	Me
c	Ph	H	Ph
d	Ph	4-NO_2	Ph
e	Ph	H	4-thiazolyl
f	Ph	4-NO_2	4-thiazolyl
g	Me	4-NO_2	4-thiazolyl
h	$(MeO)_2P{=}O$	4-NO_2	Ph
i	$(i\text{-}PrO)_2P{=}O$	4-NO_2	H
j	$(i\text{-}PrO)_2P{=}O$	4-NO_2	Ph

Scheme 2

the final product **9j**. Its UV spectrum (ethanol, $\lambda_{max} = 420$ nm) differs markedly from the spectrum of azoimine **4**. There is a doublet at $\delta = 6.5$ ($^4J_{PH} = 1.0$ Hz) in the ^1H NMR spectrum ($CDCl_3$), which makes it possible to state that the intermediate product has the structure of dihydrotriazole **8j** [$R^1 = (i\text{-}PrO)_2P{=}O$, $R^2 = 4\text{-}NO_2$, $R^3 = Ph$], (Scheme 2).

We obtained the known amidrazones **5c,i** and **11** and the unknown **5a,b,d–h,j** by the reaction of acyl halide arylhydrazones **10** with corresponding alkylamines ($H_2NCH_2R^3$) in the presence of triethylamine.[6–8] Purification of the readily oxidizable amidrazones **5a–j** is in general not necessary, and this allows the synthesis of different 1,3-di- and 1,3,5-trisubstituted 1,2,4-triazoles. Thus, 5,5′-bis(1,2,4-triazolyl) **12** has been synthesized from bisamidrazone **11**, in accordance with this method (Scheme 3).



11 Ar = $C_6H_4NO_2$-4 **12** Ar = $C_6H_4NO_2$-4

Scheme 3

The structure of triazoles **9a–j** and **12** had been confirmed by microanalytical data, IR, UV and ^1H NMR spectra.

***N*-[(4-Nitrophenylazo)(diisopropoxyphosphoryl)methylene]-*tert*-butylamine (4):**

Ag_2O (0.62 g, 2.7 mmol) was added to a solution of *N*-*tert*-butyl(diisopropoxyphosphoryl)formamide 4-nitrophenylhydrazone [**1**; $R^1 = (i\text{-}PrO)_2P(O)$, $R^2 = NO_2\text{-}4$, $R^3 = t\text{-}Bu$] in acetone (15 mL). The mixture was stirred at r.t. for 6 h. The next day the solid was separated, the acetone was removed under vacuum, and 0.7 g (70 %) of crimson-red needles were obtained by recrystallization from hexane (Table).

1-Aryl-1,2,4-triazoles 9; General Procedures:

Method A (for triazoles **9a,d,j, 12**): 30 % aq H_2O_2 (10 mL) and a few drops of sat. aq KOH was added to a stirred solution of amidrazone **5** (15 mmol) in MeCN (2–5 mL) and stirring was continued at r.t. for 1 h. The solid was separated, washed with H_2O, dried and crystallized from the appropriate solvent (Table) to give **9**.

Method B (for triazoles **9b,c,e–g**): The mixture of acyl halide arylhydrazone **10** (50 mmol) in EtOH (20 mL, for **9b,c**) or in MeCN (20 mL, for **9e–g**), of corresponding alkylamine $R^3CH_2NH_2$ (50 mmol) and of Et_3N (50 mmol) was kept at r.t. for 1–2 d. Precipitated salts were filtered. Remaining solutions were poured into H_2O. For the MeCN case, solvent was distilled and the residue was poured into H_2O. Solids were filtered, washed several times with H_2O and oxidized without further purification as described in method A.

Method C (for triazole **9i**): Amidrazone **5i** (0.3 g, 0.84 mmol) was dissolved in $CHCl_3$ (25 mL), and 30 % aq H_2O_2 (2 mL), a few drops of aq. KOH and $BnEt_3NCl$ (0.01 g) were added. The mixture was stirred at r.t. for 5 d. The layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 × 25 mL). Combined $CHCl_3$ solutions were dried (Na_2SO_4), $CHCl_3$ was removed. The residue was crystallized from CCl_4 to give **9i** (Table).

Table. Compounds **4**, **9**, **12** Prepared

Compound	Yield (%) (Method)	mp (°C)[a] (solvent)	Molecular Formula[b] or Lit. mp (°C)	UV (EtOH)[c] λ_{max} (nm) ($\log\varepsilon$)	^{1}H NMR ($CDCl_3$/TMS)[d, e] δ, J (Hz)
4	70	80–81 (hexane)	$C_{17}H_{27}NO_5P$ (398.2)	210 (4.68), 296 (4.26)	1.26 (d), 1.37 (d) and 1.43 (s, 21 H, CH_3), 4.70 (m, 2 H, CH), 7.86 (d, 2 H) and 8.24 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$)
9a	50 (A)	198–200 (EtOH)	199–201[9]	248, 312	7.33 (m, 3 H) and 8.00 (m, 2 H, Ph), 7.88 (d, 2 H) and 8.29 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$)
9b	79 (B)	140–142 (EtOH)	142[10]	–	–
9c	45 (B)	103–104 (MeOH)	104–105[11]	–	–
9d	50 (A)	165–167 (EtOH)	160–162[12]	250, 312	7.32 (10 H, 2 Ph), 7.42 (d, 2 H) and 8.05 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$)
9e	60 (B)	133–134 (ligroin/benzene, 3:1)	$C_{17}H_{12}N_4S$ (304.1)	–	7.30 (m, 8 H) and 8.10 (m, 2 H, 2 Ph), 7.77 (d, 1 H, 5-H, $J = 2.0$), 8.66 (d, 1 H, 2-H, $J = 2.0$)
9f	38 (B)	214–214.5 (EtOH)	$C_{17}H_{11}N_5O_2S$ (349.1)	250 (4.48), 309 (4.02)	7.60 (m, 3 H) and 8.20 (m, 2 H, Ph), 7.92 (d, 2 H) and 8.46 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$), 8.62 (d, 1 H, 5-H, $J = 2.0$), 9.25 (d, 1 H, 2-H, $J = 2.0$)
9g	55 (B)	201–202 ($CHCl_3$)	$C_{12}H_9N_5O_2S$ (287.1)	–	2.50 (s, 3 H, CH_3), 7.57 (d, 2 H) and 8.23 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$), 8.05 (d, 1 H, 5-H, $J = 2.0$), 8.68 (d, 1 H, 2-H, $J = 2.0$)
9h	53 (D)	117–118 (CCl_4)	$C_{16}H_{15}N_4O_5P$ (374.1)	283, 247	3.96 (d, 6 H, CH_3O, $J = 11$), 7.35 (s, 5 H, Ph), 7.45 (d, 2 H) and 8.13 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$)
9i	50 (C)	122–123 (CCl_4)	116–117[6]	–	
9j	50 (A)	119–120 (hexane/Et_2O, 1:1)	$C_{20}H_{23}N_4O_5P$ (430.2)	246 (4.61), 286 (4.54)	1.40 (d, 12 H, CH_3, $J = 6.0$), 4.83 (m, 2 H, CH), 7.45 (s, 5 H, Ph), 7.57 (d, 2 H) and 8.22 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$)
12	10 (A)	201–203 (MeOH)	$C_{28}H_{36}N_8O_{10}P_2$ (706.3)	252, 279	1.23 (d) and 1.36 (d, 12 H, CH_3, $J = 6.0$), 4.76 (m, 2 H, CH), 7.60 (d, 2 H) and 8.19 (d, 2 H, $C_6H_4NO_2$-4, $J = 9.0$)

[a] Melting points were measured with a Boetius micro mp apparatus and are not corrected.

[b] Satisfactory microanalyses obtained: C, H, N < ± 0.35.

[c] Measured using a Specord M-40 spectrophotometer.

[d] Obtained on a Varian T-60 (60 MHz) spectrometer.

[e] **9f** measured in DMSO-d_6, **9j** in CD_3CN, **4**, **12** in CCl_4.

Method D (for triazole **9h**): 2% aq. $KMnO_4$ (10.6 mL) was added to a solution of amidrazone **5h** (0.2 g, 0.53 mmol) in Et_2O (8 mL). The mixture was stirred for 2 h. Et_2O layer was separated and aqueous layers were extracted by Et_2O (10 mL). Removal of the solvent after drying (Na_2SO_4) gave a residue, which was recrystallized from CCl_4 to give **9h** (Table).

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