Synthesis and Reactions of 5-Arylamino-1,2,4-trioxans

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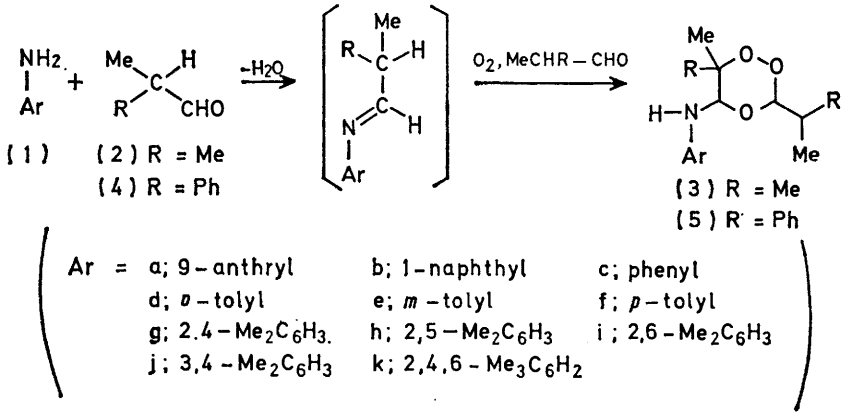
Eleven 5-arylamino-1,2,4-trioxans were synthesized by the reaction of arylamines, *e.g.*, aniline, toluidines, xylidines, or mesitylamine, with aldehydes, *e.g.*, 2-methylpropanal or 2-phenylpropanal, in the presence of atmospheric oxygen. The structures of these trioxans were proved to be similar to that of 5-(1-naphthylamino)-1,2,4-trioxan, determined by *X*-ray crystal structure analysis. Reductive decomposition of the trioxans with sodium borohydride afforded the *N*-(2-hydroxypropyl)arylamines. Pyrolysis of the trioxans gave a ketone, an aldehyde, and the *N*-formylarylamines. On decomposition with acid the trioxans gave a ketone, an aldehyde, formic acid, arylamines, and the *N*-formylarylamines. The same products were also found in the case of decomposition of the trioxans with base.

PREVIOUSLY we have reported the preparation of a crystalline chemiluminescent compound from 9-anthrylamine and 2-methylpropanal in the presence of atmospheric oxygen.[1] The structure of this compound was proposed to be the 5-(9-anthrylamino)-1,2,4-trioxan (3a) by McCapra *et al.*[2] and by Goto *et al.*[3] We also confirmed the structure of the 5-(1-naphthylamino)-1,2,4-trioxan (3b), which was obtained from 1-naphthylamine and 2-methylpropanal in the presence of atmospheric oxygen, on the basis of an *X*-ray crystal-structure analysis.[4]



SCHEME 1

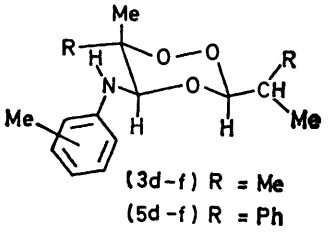
In the present paper, we report a general method for the preparation of 5-arylamino-1,2,4-trioxans from aniline, toluidines, xylidines, or mesitylamine as the arylamine, and 2-methylpropanal or 2-phenylpropanal as an aldehyde having an active hydrogen. Some fundamental reactions of these trioxans such as reductive decomposition with sodium borohohydride, pyrolysis, and acid, or base catalysed decomposition are also examined.

RESULTS AND DISCUSSION

A solution of arylamine (1) and 2-methylpropanal (2) in the hexane was kept in the dark at 30 °C for a few days in the presence of atmospheric oxygen, and the product was recrystallized from hexane. Colourless crystals of tioxans (3c, d, g, h, i, and k) were obtained in 11—66% yield (Scheme 1). In the reaction of other arylamines (1e, f, and j) with (2), the formation of a trioxan (3) was detected by the i.r. and n.m.r. spectra of the reaction mixture. However, crystalline trioxans could not be obtained because they decomposed on distillation or silica gel chromatography. A solution of an arylamine and 2-phenylpropanal (4) in hexane–ether was treated as described above, and the product was recrystallized from hexane–benzene. Colourless crystals of trioxans (5c, e, f, i, and j) were obtained in 19—53% yield (Scheme 1). In the reactions of other arylamines (1d, g, h and k) and (4), *N*-formylarylamines were obtained instead of trioxans.

Based on an *X*-ray crystal structure analysis of the 5-(1-naphthylamino)-1,2,4-trioxan (3b),[4] the trioxan ring is in the chair form, with the naphthylamino and isopropyl groups equatorial. Considering the relative orientation of the two methyl groups at C-6 and the naphthylamino-group, the methyl-group signals at δ 1.29 and 1.68 in the n.m.r. spectrum of (3b) could be assigned to the equatorial and axial methyl groups, respectively. The n.m.r. spectra of the trioxans (3c, d, g, h, i, and k) resemble very closely that of (3b) (Table), and their structures are presumed to be similar to that of (3b). Most of the n.m.r. signals of the trioxans (5), having two phenyl groups instead of the two methyl groups of trioxans (3), appear at lower field due to the ring-current

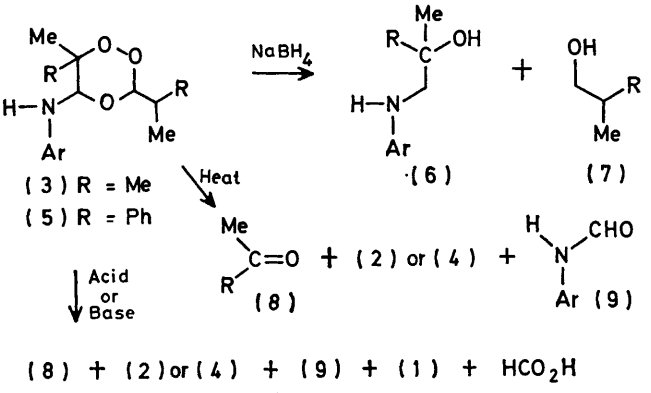
effect (Table). The signal of the C-6 methyl group of (5) appears at δ 1.78—1.87, and is therefore assumed to be axial, since the chemical shift is closer to that of the axial methyl of (3b) rather than that of the equatorial methyl.



It can be concluded that the three bulky groups, *i.e.* 1-phenylethyl, arylamino, and phenyl, are all equatorially bonded to the chair form of the trioxan ring of compounds (5). This conformation would be expected to be the more thermally stable.

In order to investigate the reactions of the trioxan ring, the following reactions of (3d) or (5e) were examined (Scheme 2). The trioxans (3d) and (5e) were reduced with sodium borohydride in ethanol to afford colourless liquids, *N*-(2-hydroxypropyl)arylamines (6), in 79 and 81% yield, respectively. Also, 2-phenylpropan-1-ol (7, R = Ph) was obtained in the reduction of (5e). The

The decomposition of the trioxan (5e) with hydrochloric acid in ethanol at room temperature was examined, and *m*-toluidine (1e) (75%), *N*-formyl-*m*-toluidine (9e) (10%), 2-phenylpropanal (4) (69%), and acetophenone (8, R = Ph) (89%) were obtained. The formation of formic acid (58%) was also confirmed. Decomposition of (3d) with hydrochloric acid afforded *o*-toluidine (1d) (67%), *N*-formyl-*o*-toluidine (9d) (28%), and formic acid



SCHEME 2 (a—k as in Scheme 1)

(28%). The formation of 2-methylpropanal (2) and acetone (8, R = Me) was also confirmed (as the 2,4-dinitrophenylhydrazones).

N.m.r. data for the trioxans (3) and (5) [δ, p.p.m. from $SiMe_4$ (multiplicity, *J*/Hz)]

	C-3			C-5		C-6		Aromatic protons	Aromatic-*Me*
	eq-Pr^i CH*Me*$_2$ (d, *J* 6—7)	eq-Pr^i C*H*Me$_2$ (m)	ax-H (d, *J* 5)	eq-NH (d, *J* 10—11)	ax-H (d, *J* 10—11)	eq-Me (s)	ax-Me (s)	(m)	(s)
(3b)	1.0	1.8	5.21	4.1	5.09	1.29	1.68	6.9—8.0 (7 H)	
(3c)	0.87	1.7	5.24	4.0	4.87	1.20	1.67	6.5—7.4 (5 H)	
(3d)	0.87	1.7	5.17	4.70	4.82	1.23	1.67	6.5—7.3 (4 H)	2.20 (3 H)
(3g)	0.95	1.8	5.13	3.67	4.86	1.18	1.52	6.6—7.1 (3 H)	2.13 (3 H), 2.22 (3 H)
(3h)	0.95	1.8	5.13	3.73	4.87	1.18	1.52	6.4—7.2 (3 H)	2.12 (3 H), 2.27 (3 H)
(3i)	0.88	1.7	5.02	3.36	4.57	1.37	1.57	7.0—7.2 (3 H)	2.37 (6 H)
(3k)	0.87	1.9	4.90	3.25	4.43	1.33	1.54	6.8—7.7 (2 H)	2.23 (3 H), 2.30 (6 H)

	C-3 *			C-5		C-6 *		Aromatic protons	Aromatic-*Me*
	eq-CHMePh CH*Me* (d, *J* 6—7)	eq-CHMePh C*H*Me (m)	ax-H (d, *J* 5)	eq-NH (d, *J* 10—11)	ax-H (d, *J* 10—11)	eq-Ph	ax-Me (s)	(m)	(s)
(5c)	1.39	3.12	5.60	4.02	5.21		1.83	6.4—8.0 (15 H)	
(5e)	1.35	3.0	5.50	3.8	5.10		1.80	6.1—8.1 (14 H)	2.12 (3 H)
(5f)	1.37	3.1	5.60	4.3	5.20		1.83	6.1—7.9 (14 H)	2.20 (3 H)
(5i)	1.30	2.9	5.33	3.3	4.63		1.87	6.4—7.8 (13 H)	1.87 (6 H)
(5j)	1.33	3.1	5.47	3.7	5.07		1.78	6.1—7.9 (13 H)	2.03 (6 H)

* The phenyl protons of the 1-phenylethyl group at C-3 and at C-6 are included in aromatic protons.

formation of (6) and (7) is explicable, as shown in Scheme 3.

Thermal decomposition of the trioxan (3d) in a sealed tube gave acetone (8, R = Me) (68%), 2-methylpropanal (2) (91%), and *N*-formyl-*o*-toluidine (9d) (84%). When the trioxan (5e) was pyrolysed, acetophenone (8, R = Ph) (83%), 2-phenylpropanal (4) (66%), and *N*-formyl-*m*-toluidine (9e) (71%) were formed. The thermal cleavage of the trioxan ring leads almost quantitatively to three carbonyl compounds, and a similar cleavage of a trioxan has been previously reported.[5]

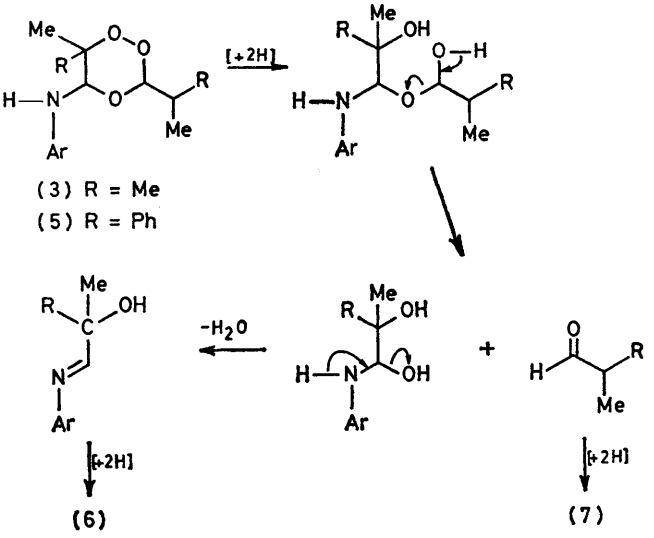
Decomposition of the trioxan (3d or 5e) with sodium ethoxide in ethanol at room temperature afforded *N*-formylarylamines (9d) (66%) or (9e) (53%), arylamines, (1d) (22%) or (1e) (18%), an aldehyde [(2) or (4)], and a ketone (8). The products are the same as those found in the acid decomposition of the trioxan.

EXPERIMENTAL

N.m.r. spectra were obtained on a Hitachi R-24B spectrometer (60 MHz) using tetramethylsilane as internal standard. I.r. spectra were measured with a Hitachi 215 spectrometer. Distillation of liquid products was carried

out in a Ball Tube Oven; bath temperatures were recorded. Gas chromatography was carried out on a Hitachi 063 instrument (2-m × 3-mm column packed with 10% polyethylene glycol 20M on Uniport B, at 80—230 °C).

Preparation of Trioxans (3).—A solution of arylamine (30 mmol) and 2-methylpropanal (90 mmol) in hexane (30 ml) was kept in the dark at 30 °C in the presence of atmospheric oxygen. After a few days the solvent was evaporated and the residue was recrystallized from hexane. Some trioxans (3d, g, and h) were obtained as colourless prisms. Other trioxans (3c, i, and k) were obtained as colourless crystals after chromatography on a short silica gel column



SCHEME 3 (a—k as in Scheme 1)

using hexane as eluant, and then recrystallization from hexane. The following compounds were recorded.

3-*Isopropyl*-6,6-*dimethyl*-5-(1-*naphthylamino*)-1,2,4-*trioxan* (3b), m.p. 79.5—80 °C (decomp.); $\nu_{max.}$ (KBr) 3 380, 1 280, 1 250, 1 150, and 1 070 cm^{-1} (Found: C, 71.85; H, 7.7; N, 4.6. $C_{18}H_{23}NO_3$ requires C, 71.75; H, 7.7; N, 4.65%): 5-*anilino*-3-*isopropyl*-6,6-*dimethyl*-1,2,4-*trioxan* (3c) (11%), m.p. 95—96 °C (decomp.); $\nu_{max.}$ (Nujol) 3 450, 1 305, 1 245, 1 145, and 1 050 cm^{-1} (Found: C, 67.1; H, 8.5; N, 5.35. $C_{14}H_{21}NO_3$ requires C, 66.9; H, 8.4; N, 5.55%); 3-*isopropyl*-6,6-*dimethyl*-5-(o-*toluidino*)-1,2,4-*trioxan* (3d) (66%), m.p. 94—97.5 °C (decomp.); $\nu_{max.}$ (Nujol) 3 440, 1 300, 1 240, 1 150, and 1 050 cm^{-1} (Found: C, 68.25; H, 8.75; N, 5.3. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.75; N, 5.3%): 3-*isopropyl*-6,6-*dimethyl*-5-(2,4-*xylidino*)-1,2,4-*trioxan* (3g) (27%), m.p. 57—58 °C (decomp.); $\nu_{max.}$ (Nujol) 3 420, 1 300, 1 270, 1 155, and 1 040 cm^{-1} (Found: C, 68.8; H, 9.2; N, 5.0. $C_{16}H_{25}NO_3$ requires C, 68.8; H, 9.0; N, 5.0%: 3-*isopropyl*-6,6-*dimethyl*-5-(2,5-*xylidino*)-1,2,4-*trioxan* (3h) (50%), m.p. 68—69 °C (decomp.); $\nu_{max.}$ (Nujol) 3 430, 1 295, 1 260, 1 150, and 1 060 cm^{-1} (Found: C, 68.8; H, 9.0; N, 5.05. $C_{16}H_{25}NO_3$ requires C, 68.8; H, 9.0; N, 5.0%); 3-*isopropyl*-6,6-*dimethyl*-5-(2,6-*xylidino*)-1,2,4-*trioxan* (3i) (11%), m.p. 58—59 °C (decomp.); $\nu_{max.}$ (Nujol) 3 410, 1 280, 1 255, 1 140, and 1 060 cm^{-1} (Found: C, 68.95; H, 8.95; N, 5.0. $C_{16}H_{25}NO_3$ requires C, 68.8; H, 9.0; N, 5.0%): and 3-*isopropyl*-5-*mesitylamino*-6,6-*dimethyl*-1,2,4-*trioxan* (3k) (25%), m.p. 58—59 °C (decomp.); $\nu_{max.}$ (Nujol) 3 400, 1 300, 1 225, 1 155, and 1 050 cm^{-1} (Found: C, 69.6; H, 9.35; N, 4.9. $C_{17}H_{27}NO_3$ requires C, 69.6; H, 9.25; N, 4.75%).

Preparation of Trioxans (5).—A solution of arylamine (20 mmol) and 2-phenylpropanal (60 mmol) in hexane–ether (45 ml, 8 : 1) was auto-oxidized with atmospheric oxygen. After a few days the solvent was evaporated and the residue was recrystallized from hexane–benzene (1 : 1). Trioxans (5c, e, f, i, and j) were obtained as colourless needles: 5-*anilino*-6-*methyl*-6-*phenyl*-3-(1-*phenylethyl*)-1,2,4-*trioxan* (5c) (22%), m.p. 116—117 °C (decomp.); $\nu_{max.}$ (Nujol) 3 460, 1 300, 1 250, 1 150, and 1 055 cm^{-1} (Found: C, 76.8; H, 6.7; N, 3.75. $C_{24}H_{25}NO_3$ requires C, 76.75; H, 6.6; N, 3.75%): 6-*methyl*-6-*phenyl*-3-(1-*phenylethyl*)-5-(m-*toluidino*)-1,2,4-*trioxan* (5e) (53%), m.p. 94—95.5 °C (decomp.); $\nu_{max.}$ (Nujol) 3 450, 1 295, 1 265, 1 060, and 1 050 cm^{-1} (Found: C, 76.55; H, 6.95; N, 3.6. $C_{25}H_{27}NO_3$ requires C, 77.1; H, 7.0; N, 3.6%): 6-*methyl*-6-*phenyl*-3-(1-*phenylethyl*)-5-(p-*toluidino*)-1,2,4-*trioxan* (5f) (29%), m.p. 86—87 °C (decomp.); $\nu_{max.}$ (Nujol) 3 450, 1 290, 1 260, 1 140, and 1 050 cm^{-1} (Found: C, 76.2; H, 6.8; N, 3.55. $C_{25}H_{27}NO_3$ requires C, 77.1; H, 7.0; N, 3.6%): 6-*methyl*-6-*phenyl*-3-(1-*phenylethyl*)-5-(2,6-*xylidino*)-1,2,4-*trioxan* (5i) (36%), m.p. 95—96.5 °C (decomp.); $\nu_{max.}$ (Nujol) 3 390, 1 335, 1 255, 1 140, and 1 065 cm^{-1} (Found: C, 77.5; H, 7.15; N, 3.55. $C_{26}H_{29}NO_3$ requires C, 77.4; H, 7.25; N, 3.45%): and 6-*methyl*-6-*phenyl*-3-(1-*phenylethyl*)-5-(3,4-*xylidino*)-1,2,4-*trioxan* (5j) (19%), m.p. 106—107 °C (decomp.); $\nu_{max.}$ (Nujol) 3 450, 1 300, 1 260, 1 150, and 1 050 cm^{-1} (Found: C, 77.3; H, 7.1; N, 3.4. $C_{26}H_{29}NO_3$ requires C, 77.4; H, 7.25; N, 3.45%).

Reduction with Sodium Borohydride.—Sodium borohydride (0.19 g) was added to a stirred solution of (3d) (1.33 g) in ethanol (80 ml). The mixture was heated at 60 °C for 30 min and then water (20 ml) was added with stirring. After evaporation of ethanol, the product was extracted with ether. The oily product after removal of ether was chromatographed on a silica gel column [benzene–ethyl acetate (5 : 1)]. After removal of the solvent the residue was distilled at 116 °C and 5 mmHg to yield N-(2-*hydroxy*-2-*methylpropyl*)-o-*toluidine* (6, R=Me) (0.17 g, 79%); $\delta(CDCl_3)$ 1.22 (6 H, s, *gem*-Me_2), 2.12 (3 H, s, Ar-*Me*), 3.02 (2 H, s, CH_2–N), 3.1 (2 H, br s, OH and NH), and 6.5—7.5 (4 H, m, Ar-H); $\nu_{max.}$ (neat) 3 550, 3 440, 1 150, and 740 cm^{-1} (Found: C, 73.0; H, 9.5; N, 7.85. $C_{11}H_{17}NO$ requires C, 74.7; H, 9.55; N, 7.8%).

The trioxan (5e) (0.97 g) was reduced with sodium borohydride (0.1 g) in ethanol (80 ml) as described previously. Distillation of the reaction mixture at 5 mmHg gave fraction A (b.p. 95—110 °C), fraction B (b.p. 120—130 °C), and a residue. Fraction A was purified by chromatography on silica gel [benzene–ethyl acetate (5 : 1)] to give 2-*phenylpropan*-1-*ol* (0.26 g, 76%). Chromatography of fraction B [on silica gel; benzene–ethyl acetate (5 : 1)] gave N-(2-*hydroxy*-2-*phenylpropyl*)-m-*toluidine* (6, R = Ph) (0.49 g, 81%); $\delta(CDCl_3)$ 1.55 (3 H, s, Me), 2.23 (3 H, s, Ar-*Me*), 3.07 (2 H, br s, OH and NH), 3.42 (2 H, s, CH_2–N), and 6.3—7.6 (9 H, m, Ar-H); $\nu_{max.}$ (neat) 3 550, 3 420, 1 100, 760, and 700 cm^{-1} (Found: C, 79.45; H, 7.75; N, 5.75. $C_{16}H_{19}NO$ requires C, 79.65; H, 7.95; N, 5.8%).

Pyrolysis.—Crystals of (3d) (0.50 g) were decomposed in a sealed tube at 110 °C for 15 min. The n.m.r spectrum showed the distillate (0.20 g) to be a mixture of acetone (8, R = Me) and 2-methylpropanal (2) in a *ca.* 3 : 5 ratio. The solid residue was recrystallized from benzene–hexane (1 : 2), as colourless needles (0.21 g, 84%), which proved to be

identical with an authentic sample of *N*-formyl-*o*-toluidine (9d).

Crystals of (5e) (0.97 g) were decomposed in a sealed tube at 110 °C for 15 min. Analysis of the product by gas chromatography using ethylbenzene as internal standard showed it to be a mixture of acetophenone (8, R = Ph) (83%), 2-phenylpropanal (4) (66%), and *N*-formyl-*m*-toluidine (9e) (71%) [percentages based on starting amount of (5e)].

Decomposition with Hydrochloric Acid.—The trioxan (5e) (1.30 g) was stirred at room temperature for 5 min with a solution of 6N hydrochloric acid (1.5 ml) in ethanol (50 ml). After neutralization with sodium hydroxide, analysis of the reaction mixture by gas chromatography showed the presence of *m*-toludine (1e) (75%), *N*-formyl-*m*-toluidine (9e) (10%), acetophenone (8, R = Ph) (89%), and 2-phenylpropanal (4) (69%) (percentages based on starting material). The solution was diluted with water (30 ml) and made basic with sodium hydroxide. After evaporation of ethanol, the alkaline aqueous solution was extracted with ether and the aqueous solution was evaporated to dryness. The resulting solid was treated with *p*-toluidine by the method of Shriner,[6] and colourless needles of *N*-formyl-*p*-toluidine (0.26 g) were obtained, evidence for the existence of formic acid (58%) in the reaction mixture.

To a solution of trioxan (3d) (0.88 g) in ethanol (50 ml), 6N hydrochloric acid (1.5 ml) was added with stirring. After neutralization, analysis of the reaction mixture by gas chromatography showed *o*-toluidine (1d) (67%) and *N*-formyl-*o*-toluidine (9d) (28%). The solution was diluted with water (30 ml) and distilled at 78 °C and atmospheric pressure. The distillate was treated with 2,4-dinitrophenylhydrazine (1.32 g), and the red precipitate of hydrazones obtained was purified by preparative t.l.c. on silica gel, and shown to be identical with authentic samples of the 2,4-dinitrophenylhydrazones of acetone and 2-methylpropanal by i.r. spectral comparison. The residual aqueous solution from the distillation was washed with ether, evaporated to dryness, and treated with *p*-toluidine. The formation of *N*-formyl-*p*-toluidine (0.13 g) showed the presence of formic acid (28%).

Decomposition with Sodium Ethoxide.—The trioxan (5e) (1.30 g) was stirred at room temperature for 5 min with a solution of sodium (0.15 g) in ethanol (120 ml). After neutralization, analysis of the reaction mixture by gas chromatography showed *N*-formyl-*m*-toluidine (9e) (53%), *m*-toluidine (1e) (18%), acetophenone (8, R = Ph) (91%), and 2-phenylpropanal (4) (80%) [percentages based on (5e)]. The trioxan (3d) (0.88 g) was stirred with a solution of sodium (0.15 g) in ethanol (60 ml), and analysis, after neutralization, of the reaction mixture by gas chromatography showed the presence of *N*-formyl-*o*-toluidine (9d) (66%) and *o*-toluidine (1d) (18%). 2-Methylpropanal and acetone were also obtained as their 2,4-dinitrophenylhydrazones.

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