

Heterocycles in Organic Synthesis. Part 23.¹ 1-Amino-4,6-diphenyl-2-pyridone: a New Reagent for the Conversion of Aldehydes into Nitriles²

By Alan R. Katritzky* and Pedro Molina-Buendia, School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ

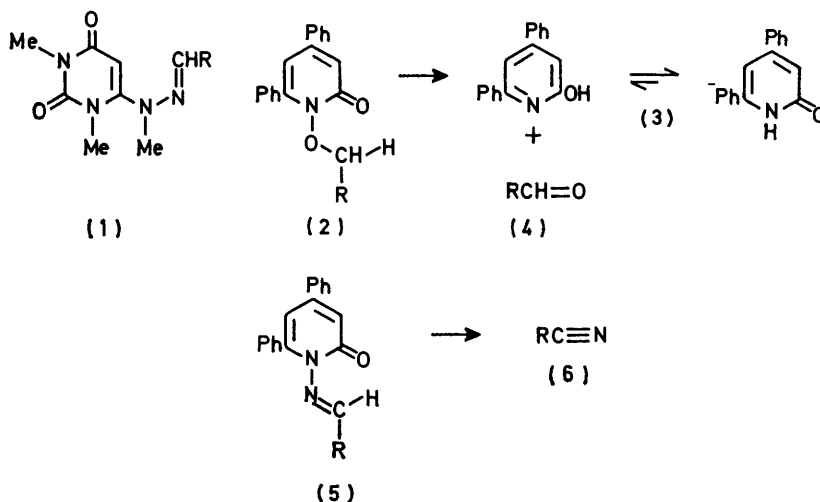
The title compound (9) with aldehydes yields imines which are smoothly pyrolysed in high yield to nitriles. Orthoformates react with (9) to give the corresponding ethers which thermolyse mainly by alkyl-transfer or alpha-elimination. Acylation of (9) gives the acylamino-derivatives which on heating form the corresponding isocyanates in 85–95% yield.

MANY methods are available for the conversion of aldehydes into nitriles.³ In recent years the classical synthesis from aldoximes has been improved by the introduction of new dehydrating agents: 1,1'-dicarbonylbi-imidazole,⁴ phenyl chloroformate,⁵ phosgeneimmonium chloride,⁶ trichloroacetonitrile,⁷ 2,4-dinitrofluorobenzene,⁸ dicyclohexylcarbodi-imide (with⁹ or without¹⁰ Cu²⁺), oxime anions,¹¹ phenyl chlorosulphite,¹² trifluoromethanesulphonic anhydride,¹³ S-methyl-*NN*-dimethylthioformimidinium salts,⁸ Ph₃P-CCl₄,¹⁴ and dialkyl hydrogen phosphonates.¹⁵ Other recent methods have allowed aldehydes to react with *O*-substituted hydroxylamine derivatives in one or two step sequences: *O*-(2,4-dinitrophenyl)hydroxylamine,¹⁶ *ON*-bistrifluoroacetylhydroxylamine,¹⁷ and hydroxylamine *O*-sulphonic acid.¹⁸

of aldehyde synthesis; we now describe the analogous sequence (5)→(3) + (6) as a useful nitrile preparative method.

The Preparation of Imines of 1-Amino-4,6-diphenyl-2-pyridone.—1-Amino-4,6-diphenyl-2-pyridone (9) has been reported by two groups,^{25,26} in each case from hydrazine and the pyrone (7) in yields of ca. 35%; in our hands this method gave a 60% yield, alternatively it could be made from the thiapyrone (8) in 87% yield. El-Kholy *et al.* reported²⁵ the reaction of (9) with benzaldehyde to yield the imine (5; R = Ph), and we find that this transformation proceeds smoothly with a variety of aldehydes: yields were mostly >90% (Table 1). Analogous compounds from other 1-amino-2-pyridones have been described.²⁷

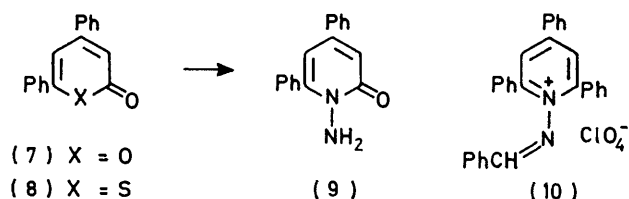
Thermolysis of the imines (5) gave the corresponding



Less attention has been paid to the use of hydrazine derivatives for this conversion, although H₂O₂ oxidation of RCH:N·NRR₂,¹⁹ photolytic oxidation of RCH:N·NPh₂,²⁰ base treatment of RCH:N·NMe₃⁺,²¹ and thermolysis of imines from 1-amino-1,2,4-triazole²² and the uracil derivatives (1)²³ are all reported to give the corresponding nitriles.

All the above methods employ acidic, basic, oxidising, hydrolysing, or acylating conditions. The conversion RCH:N·X → RCN needs the fission of the C-H bond; if this could be achieved by an intramolecular transfer, milder conditions might be achievable. We recently reported²⁴ the thermolysis (2)→(3) + (4) as a method

nitriles in yields of 71–97% (Table 2), thus constituting a practical procedure for the conversion of amines to



nitriles. A conceptually similar method, reaction of ditosylimides with dimethyl sulphoxide has failed;²⁸

TABLE 1

Physical and analytical data for imines (5) from 1-amino-4,6-diphenyl-2-pyridone

R in (5)	Yield (%)	Solvent for cryst.*	M.p. (°C)	Molecular formula	Found			Required		
					C	H	N	C	H	N
Ph	99	EtOH	179—180	C ₂₄ H ₁₆ N ₂ O	82.1	5.2	7.8	82.2	5.2	8.0
<i>p</i> -Me·C ₆ H ₄	95	EtOH	183	C ₂₅ H ₂₀ N ₂ O	82.4	5.4	7.9	82.4	5.5	7.8
<i>p</i> -MeO·C ₆ H ₄	97	EtOH	181	C ₂₅ H ₂₀ N ₂ O ₂	78.8	5.3	7.3	78.9	5.2	7.3
<i>p</i> -O ₂ N·C ₆ H ₄	95	AcOEt	257—258	C ₂₄ H ₁₇ N ₃ O ₃	72.7	4.3	10.7	72.9	4.3	10.6
C ₆ H ₅ -CH=CH-	60	EtOH	174	C ₂₆ H ₂₀ N ₂ O	82.8	5.4	7.4	82.9	5.3	7.4
2-Furyl	93	EtOH	187	C ₂₂ H ₁₆ N ₂ O ₂	77.6	4.7	8.2	77.6	4.7	8.2
3-Pyridyl	81	C ₆ H ₆	220 (decomp.)	C ₂₃ H ₁₇ N ₃ O	78.5	4.9	12.0	78.6	4.9	12.0
3,4-Dimethoxyphenyl	95	EtOH	185	C ₂₆ H ₂₂ N ₂ O ₃	76.0	5.4	6.7	76.1	5.4	6.8

* All crystallised as yellow plates.

Russian authors²⁹ have briefly reported that benzonitrile was obtained by the thermolysis of the imine (10) obtained *in situ* from benzaldehyde azine and triphenylpyrylium perchlorate.

TABLE 2

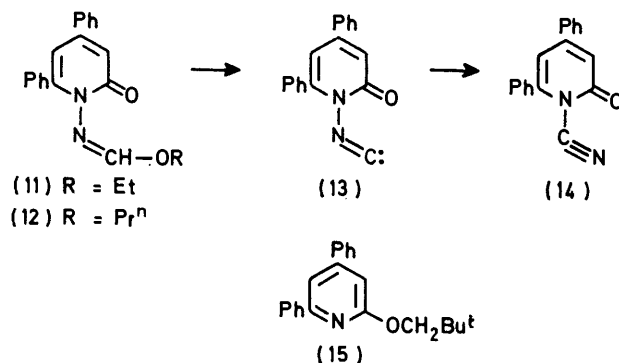
Thermolysis of the imines (5) to nitriles

R in (5)	t/min	T(°C)	Yield ^a	M.p. (°C)
<i>n</i> -C ₃ H ₇	60	200	71	<i>b</i>
Ph	60	220	94	<i>b</i>
<i>p</i> -Me·C ₆ H ₄	60	220	90	<i>b</i>
<i>p</i> -MeO·C ₆ H ₄	60	220	72	60
<i>p</i> -NO ₂ ·C ₆ H ₄	60	260	85	(61—62) ^e 147 (149) ^d
PhCH=CH	60	250	69	<i>b</i>
3-Furyl	60	220	73	<i>b</i>
3-Pyridyl	45	230	97	51
3,4-(MeO) ₂ C ₆ H ₃	45	200	95	(50—52) ^e 68 (67—68) ^f

^a Of nitriles. ^b Oil; compound identified by i.r. spectral comparison with authentic material. ^c 'Handbook of Chemistry and Physics,' 51st edn., ed. R. C. Weast, Chemical Rubber Co., Cleveland, Ohio, 1970—1971, p. C-189; (*d*) p. C-192; (*e*) p. C-468; (*f*) p. C-183.

Reactions of (5) with Orthoformates.—We attempted to extend our synthesis by the preparation of compounds of type (11). The aminopyridone (9) reacted with triethyl and tri-*n*-propyl orthoformates to give the corresponding

(15) (83%); presumably the other product is HNCO and the reaction may be concerted.



Acylation of 1-Amino-4,6-diphenyl-2-pyridone.—Compound (9) was readily acylated to give the corresponding 1-acylamino-pyridones (16) (Table 3) which on heating at 180 °C with some 4,6-diphenyl-2-pyridone as flux give the corresponding isocyanates (17) with liberation of more of the pyridone (Table 4). We have recently shown³⁰ that the thermolysis of (18) gives isocyanate in good yield: the present reaction is clearly related.

El-Kholy *et al.*^{27b} reported the diacylation of 1-amino-4,6-diphenyl-5-phenoxy-2-pyridone: we have found that

TABLE 3

1-Acylamino-4,6-diphenyl-2-pyridones (16)^a

R in (16)	Yield (%)	M.p. (°C)	Molecular formula	Found (%)			Required (%)		
				C	H	N	C	H	N
Me	72	215—220 (decomp.)	C ₁₈ H ₁₆ N ₂ O ₂	74.8	5.5	9.0	75.0	5.3	9.2
Ph	73	305—310 (decomp.)	C ₂₄ H ₁₈ N ₂ O ₂	78.6	5.1	7.5	78.7	5.0	7.7
PhCH:CH	71	275—280 (decomp.)	C ₂₆ H ₂₀ N ₂ O ₂	79.5	5.3	7.4	79.6	5.1	7.1
<i>p</i> -Cl·C ₆ H ₄	74	290—295 (decomp.)	C ₂₄ H ₁₇ ClN ₂ O ₂	71.9	4.2	6.9	71.9	4.2	7.0
<i>p</i> -Me·C ₆ H ₄	85	260—263 (decomp.)	C ₂₅ H ₂₀ N ₂ O ₂	78.7	5.2	7.1	78.9	5.3	7.4

^a All these compounds crystallised as needles from chloroform—light petroleum.

imino-ethers (11) and (12) in 83 and 75% yield respectively. Pyrolysis of these imino-ethers was expected to yield the alkyl cyanates by a reaction of type (2)→(3) + (4); although some evidence was obtained for this as a minor pathway, the major products were the corresponding ethyl or *n*-propyl alcohol and 1-cyano-4,6-diphenyl-2-pyridone (14). Evidently an alpha-elimination occurs and the isonitrile (13) rearranges to (14).

Trineopentyl orthoformate reacts with the amino-pyridone (9) to give 2-neopentoxy-4,6-diphenylpyridine

our monoacyl derivatives (16) can also be prepared by mild hydrolysis of such bisacyl compounds.

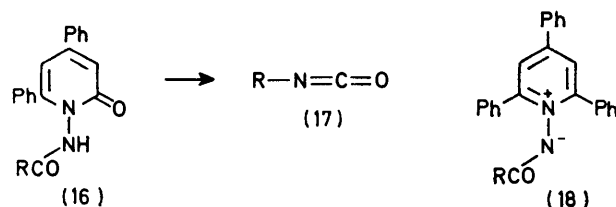


TABLE 4
Pyrolysis^a of 1-acylamino-derivatives

R	Yield isocyanate (%) ^b	Urea		Ref.
		M.p. (°C)	Lit. m.p. (°C)	
Me	95	153	152—153	c
Ph	90	238	237—237.5	d
PhCH:CH	85	211	217	e
<i>p</i> -Cl·C ₆ H ₄	87	299	297—299 ^f	g
<i>p</i> -Me·C ₆ H ₄	89	218	218	g

^a Pyrolysis conditions: 30 min at 180 °C. ^b Characterised as ureas with aniline. ^c Beilsteins Handbuch der Organischen Chemie, Suppl. 2, ed. F. Richter, Springer-Verlag, Berlin, 1950, vol. 12, p. 205. ^d Footnote c, p. 207. ^e Beilsteins Handbuch der Organischen Chemie, eds. B. Prager, P. Jacobson, P. Schmidt, and D. Stern, Springer-Verlag, Berlin, 1929, vol. 12, p. 355. ^f Characterised as urea with *p*-toluidine. ^g Footnote c, p. 512.

EXPERIMENTAL

4,6-Diphenyl-2-pyrone.—Ethyl benzoylacetate (132 g, 680 mmol) and concentrated H₂SO₄ (132 g, 1.34 mol) were kept at 20 °C for 3 weeks. The dark green viscous mass was poured on ice to give 4,6-diphenyl-2-pyrone (32.9 g, 39%) which crystallised from EtOH, m.p. 138 °C (lit.,³¹ 138—138.5 °C).

4,6-Diphenyl-1,2-dithiopyrone.—Molecular sieves (Linde 5 A, 400 g) acetophenone (120 g, 100 mmol), pyrrolidine (84 g, 120 mmol), and dry benzene (400 ml) were shaken for 48 h (no free ketone was detected by n.m.r.). Solvent was removed and carbon disulphide (200 ml) was added with stirring during 10 min to the residual 1-phenyl-1-pyrrolidinylethylene in dioxan (200 ml). After the mixture had been stirred for 1 h the excess of CS₂ was removed by distillation and a mixture of MeOH (40 ml) and H₂O (160 ml) added. Chloroform extracted the 4,6-diphenyl-1,2-dithiopyrone (75 g, 54%), which crystallised as needles from dioxan-MeOH, m.p. 113 °C (lit.,³² 113 °C).

4,6-Diphenyl-1,2-dithiopyrone (21 g, 75 mmol) in dry toluene (450 ml) was added with slow stirring to PCl₅ (31.27 g, 150 mmol) in dry toluene (1 500 ml). After 1.5 h under reflux 2-chloro-4,6-diphenyl-1-thiopyrylium chloride (22.6 g, 94%) separated, m.p. 113 °C (lit.,³³ 105—115 °C).

2-Chloro-4,6-diphenyl-1-thiopyrylium chloride (20.6 g, 64 mmol), AcOH (10 ml), and benzylamine (26 ml, 230 mmol) were boiled for 30 min and then poured into ice-water to give crude 4,6-diphenyl-1-thio-2-pyrone, which crystallised as yellow needles (13 g, 76%), m.p. 98 °C (lit.,³³ 101 °C) from dilute MeOH.

1-Amino-4,6-diphenyl-2-pyridone.—(i) 4,6-Diphenyl-2-pyrone (30 g, 150 mmol) in EtOH (500 ml) was refluxed with hydrazine hydrate (120 ml, 99%) for 4 h. Dilution with ice-water gave the 2-pyridone (18 g, 60%), which yielded needles, m.p. 166 °C (lit.,^{25,26} 164—166 °C), from benzene-light petroleum (1 : 1). (ii) 1-Thio-4,6-diphenyl-2-pyrone reacted under the same conditions to give the same 1-amino-2-pyridone, m.p. and mixed m.p. 165 °C (87%).

General Procedure for 1-(Alkylideneamino)-4,6-diphenyl-2-pyridones (5) (Table 1).—1-Amino-4,6-diphenyl-2-pyridone (11 mmol, 2.88 g), the aldehyde (11 mmol), and EtOH (15 ml) were heated to reflux for 4 h. After 24 h at 20 °C the precipitate was recrystallised.

Ethyl N-(2-Oxo-4,6-diphenyl-1-pyridyl)formimidate (11).—1-Amino-4,6-diphenyl-2-pyridone (250 mg, 0.95 mmol) and triethyl orthoformate (1 g, 6.7 mmol) were heated for 12 h at 140 °C. Excess of triethyl orthoformate was

removed at 60 °C/30 mmHg. The residue gave the ethyl formimidate (0.25 g, 83%) as yellow microcrystals from benzene-light petroleum, m.p. 90 °C (Found: C, 75.7; H, 5.8; N, 8.6. C₂₀H₁₈N₂O₂ requires C, 75.5; H, 5.7; N, 8.8%); ν_{\max} (Nujol) 3 030, 1 665, 1 615, 1 590, 1 570, 1 535, 1 490, 1 270, 850, 770, 760, 710, and 695 cm⁻¹; δ (CDCl₃, 60 MHz) 8.3 (1 H, s), 7.4 (10 H, s), 6.9 (1 H, d), 6.45 (1 H, d), 4.15 (2 H, q), and 1.3 (3 H, t).

***n*-Propyl N-(2-Oxo-4,6-diphenyl-1-pyridyl)formimidate (12) (75%)** [prepared by the same method as (11)] formed yellow microcrystals, m.p. 83 °C, from benzene-light petroleum (Found: C, 76.0; H, 6.2; N, 8.4. C₂₁H₂₀N₂O₂ requires C, 75.9; H, 6.1; N, 8.4%); ν_{\max} (Nujol) 3 050, 3 030, 1 660, 1 610, 1 590, 1 570, 1 530, 1 490, 1 265, 850, 760, and 700 cm⁻¹; δ (CDCl₃, 60 MHz) 8.3 (1 H, s), 7.35 (10 H, s), 6.9 (1 H, d), 6.4 (1 H, d), 4.0 (2 H, t), 1.5 (2 H, m), and 0.8 (3 H, t).

2-Neopentoxy-4,6-diphenylpyridine (15).—1-Amino-4,6-diphenyl-2-pyridone (250 mg, 0.95 mmol) and trineopentyl orthoformate (1 g, 3.6 mmol) were heated at 140 °C overnight. Neopentyl alcohol was removed at 110 °C/10 mmHg, and EtOH (5 ml) added. At 0 °C the 2-neopentoxy-4,6-diphenylpyridine separated. Recrystallisation from EtOH gave microcrystals (250 mg, 83%), m.p. 54 °C (Found: C, 83.1; H, 7.1; N, 4.4. C₂₂H₂₃NO requires C, 83.2; H, 7.3; N, 4.4%); ν_{\max} (Nujol) 3 080, 3 060, 3 030, 1 610, 1 600, 1 590, 1 550, 1 500, 1 405, 1 200, 1 000, 860, 770, 760, and 690 cm⁻¹; δ (CDCl₃, 60 MHz) 8.0 (1 H, s), 7.4 (10 H, m), 6.8 (1 H, s), 4.5 (2 H, s), and 0.9 (9 H, s).

Pyrolysis of Ethyl N-(2-Oxo-4,6-diphenyl-1-pyridyl)formimidate.—The formimidate (2 g, 6 mmol) was heated at 190 °C/2 mmHg, for 15 min. EtOH was distilled off, and the residue crystallised from EtOH to give 1-cyano-4,6-diphenyl-2-pyridone (1.45 g, 85%) as microcrystals, m.p. 157 °C (Found: C, 79.2; H, 4.5; N, 10.3. C₁₈H₁₂N₂O requires C, 79.4; H, 4.4; N, 10.3%); ν_{\max} (Nujol) 3 040, 3 030, 2 240, 1 685, 1 610, 1 575, 1 535, 1 490, 1 350, 1 255, 840, 750, and 695 cm⁻¹; δ (CDCl₃, 60 MHz) 7.55 (10 H, s), 6.75 (1 H, s), and 6.5 (1 H, s).

***n*-Propyl N-(2-oxo-4,6-diphenyl-1-pyridyl)formimidate** pyrolysed under similar conditions to give *n*-propanol and 1-cyano-4,6-diphenyl-2-pyridone (83%), m.p. 157 °C.

General Procedure for Preparation of 1-Acylamino-4,6-diphenyl-2-pyridones (16) (Table 3).—1-Amino-4,6-diphenyl-2-pyridone (2.88 g, 11 mmol), the acyl chloride (22 mmol) and anhydrous sodium carbonate (8 g) were refluxed in dry chloroform (60 ml) for 2 h. 2M-Hydrochloric acid (200 ml) was added and the solid treated with 5% methanolic potassium hydroxide (100 ml) for 2 h. Reacidification gave the 1-acylamino-4,6-diphenyl-2-pyridones.

General Procedure for Pyrolysis of 1-Acylamino-4,6-diphenyl-2-pyridones (16) (Table 4).—The 1-acylamino-compound (5 g) and 4,6-diphenyl-2-pyridone (0.3 g) were heated at 180 °C/1 mmHg. The residue was 4,6-diphenyl-2-pyridone while the isocyanates distilled and were characterised by spectral data and as the urea.

One of us (P. M. B.) would like to thank M.E.C. of Spain for a Postdoctoral Research Fellowship.

[8/1318 Received, 17th July, 1978]

REFERENCES

1 Part 22, A. R. Katritzky, U. Gruntz, N. Mongelli, and M. C. Rezende, preceding paper.

- ² Preliminary communication of part of this work: J. B. Bapat, R. J. Blade, A. J. Boulton, J. Épsztajn, A. R. Katritzky, J. Lewis, P. Molina-Buendia, P.-L. Nie, and C. A. Ramsden, *Tetrahedron Letters*, 1976, 2691.
- ³ For a review of the earlier literature see Yu. A. Naumov and I. I. Grandberg, *Russian Chem. Rev.*, 1966, **35**, 9.
- ⁴ H. G. Foley and D. R. Dalton, *J.C.S. Chem. Comm.*, 1973, 628.
- ⁵ J. M. Prokipcak and P. A. Forte, *Canad. J. Chem.*, 1971, **49**, 1321.
- ⁶ V. P. Kukhar and V. I. Pasternak, *Synthesis*, 1974, 563.
- ⁷ T.-L. Ho and C. M. Wong, *J. Org. Chem.*, 1973, **38**, 2241.
- ⁸ T.-L. Ho and C. M. Wong, *Synth. Comm.*, 1975, **5**, 299.
- ⁹ E. Vowinkel and J. Bartel, *Chem. Ber.*, 1974, **107**, 1221.
- ¹⁰ T.-L. Ho, *Synth. Comm.*, 1973, **3**, 101.
- ¹¹ R. D. Knudsen, A. G. Morrice, and H. R. Snyder, *J. Org. Chem.*, 1975, **40**, 2878.
- ¹² J. G. Krause and S. Shaikh, *Synthesis*, 1975, 502.
- ¹³ J. B. Hendrickson, K. W. Bair, and P. M. Keehn, *Tetrahedron Letters*, 1976, 603.
- ¹⁴ R. Appel, R. Kleinstück, and K.-D. Ziehn, *Chem. Ber.*, 1971, **104**, 2025.
- ¹⁵ P. J. Foley, jun., *J. Org. Chem.*, 1969, **34**, 2805.
- ¹⁶ M. J. Miller and G. M. Loudon, *J. Org. Chem.*, 1975, **40**, 126.
- ¹⁷ J. H. Pomeroy and C. A. Craig, *J. Amer. Chem. Soc.*, 1959, **81**, 6340.
- ¹⁸ C. Fizet and J. Streith, *Tetrahedron Letters*, 1974, 3187; J. Streith, C. Fizet, and H. Fritz, *Helv. Chim. Acta*, 1976, **59**, 2786.
- ¹⁹ R. F. Smith, J. A. Albright, and A. M. Waring, *J. Org. Chem.*, 1966, **31**, 4100.
- ²⁰ R. W. Binkley, *Tetrahedron Letters*, 1970, 2085.
- ²¹ R. F. Smith and L. E. Walker, *J. Org. Chem.*, 1962, **27**, 4372; cf. also R. F. Smith and K. J. McGrath, *J. Org. Chem.*, 1976, **41**, 395.
- ²² H. G. O. Becker and H. J. Timpe, *Z. Chem.*, 1964, **4**, 304.
- ²³ F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, 1975, **48**, 1484.
- ²⁴ M. J. Cook, A. R. Katritzky, and G. H. Millet, *Heterocycles*, 1977, 227.
- ²⁵ I. E.-S. El-Kholy, F. K. Rafla, and M. M. Mishrikey, *J. Chem. Soc. (C)*, 1970, 1578.
- ²⁶ C. W. Rees and M. Yelland, *J.C.S. Perkin I*, 1972, 77.
- ²⁷ See, e.g., (a) I. E.-S. El-Kholy and F. K. Rafla, *J. Chem. Soc. (C)*, 1969, 974; (b) I. E.-S. El-Kholy, F. K. Rafla, and G. Soliman, *J. Chem. Soc.*, 1961, 4490.
- ²⁸ N. H. Andersen and H. Uh, *Synth. Comm.*, 1972, **2**, 297.
- ²⁹ G. N. Dorofeyenko, E. A. Zvezdina, M. P. Zhdanova, V. V. Derbenev, Ye. S. Matkovskaya, *Khim. Geterotsikl. Soedinenii*, 1974, 1036.
- ³⁰ A. R. Katritzky, J. Lewis, and P.-L. Nie, *J.C.S. Perkin I*, 1979, 446.
- ³¹ F. Arndt and B. Eistert, *Chem. Ber.*, 1925, **58**, 2318.
- ³² R. Mayer and J. Wehl, *Angew. Chem. Internat. Edn.*, 1965, **4**, 246.
- ³³ J. Faust, G. Speier, and R. Mayer, *J. prakt. Chem.*, 1969, **311**, 61.