New Synthesis of Fused Pyrimidine Derivatives *via ortho*-(Isocyanomethyl)nitroaromatic Compounds

J. Chem. Research (S), 1998, 14–15
J. Chem. Research (M), 1998, 0180–0187

Stanisław Ostrowski*

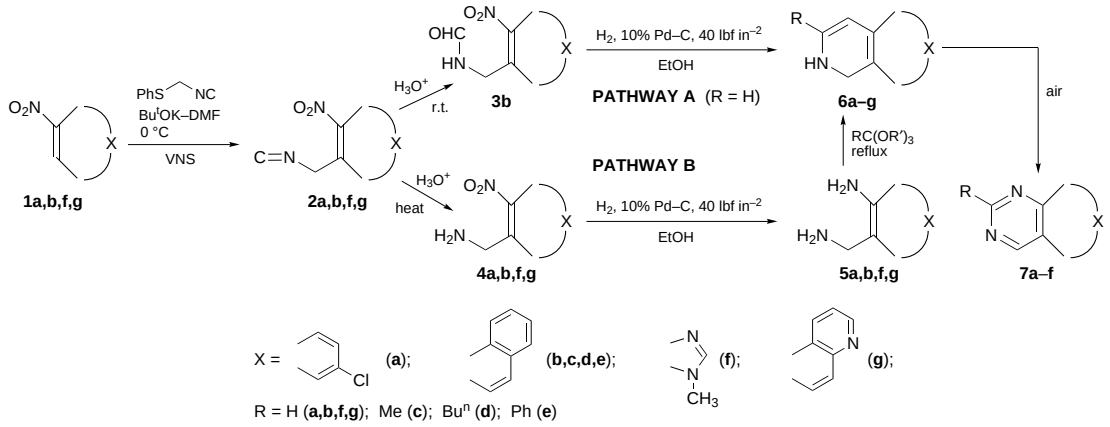
Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, PL 01-224 Warszawa, Poland

An efficient synthesis of functionalized fused pyrimidine derivatives from the respective *ortho*-(isocyanomethyl)nitroarenes is described: hydrolysis of the isocyano group in the title isocyanides followed by catalytic reduction of the nitro group and subsequent cyclocondensation of the diamine formed with orthoesters leads to the final products.

Since the early years of this century several studies on the synthesis and structure–activity relationships of pyrimidine derivatives have been reported.[1,2] A pyrimidine nucleus is embedded in a large number of alkaloids, drugs, antibiotics, agrochemicals and antimicrobial agents.[1] In addition, many simple fused pyrimidines (purines, pteridines) are biologically active by themselves[2b,c] or are essential components of very important naturally occurring substances.

The availability of starting materials has been a limiting factor for the preparation of fused pyrimidine derivatives[8,9] such as quinazolines and various tricyclic heteroaromatic compounds. Many of these products can be easily synthesized from the corresponding *ortho*-aminobenzylamines or their fused heteroanalogues.[10] However, the rather difficult access to these key intermediates[11a,b] or to their precursors[11c] is a serious limitation for this synthesis.

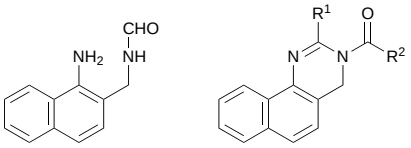
We have described lately[12] a general method for the synthesis of *ortho*-isocyanomethyl nitro-aromatic/heteroaromatic compounds of type **2** (Scheme), based on the Vicarious Nucleophilic Substitution (VNS) of hydrogen. In this work a practical application of the above method for the synthesis of fused pyrimidines is described. One can expect that the wide spectrum of nitroarenes available as starting materials will broaden considerably the frontiers of this synthesis.



Scheme

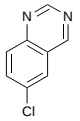
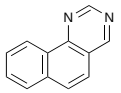
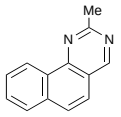
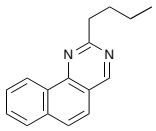
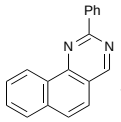
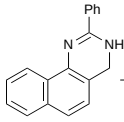
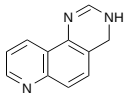
The desired *ortho*-(*N*-formylaminomethyl)nitroaromatic compounds of type **3** or diamino intermediates **5** were efficiently obtained from the above isocyanides **2**. Hydrolysis of these isocyanides under mild conditions (MeOH–H_2O, catalytic amount of HCl, room temperature, 10 h) gave formamides such as **3b**. Subsequent reduction of the nitro group (10% Pd–C, 40 lbf in^{-2}, EtOH, 4 h) followed by cyclisation was expected to afford a pyrimidine derivative of type **6** (Pathway A). Instead, this model compound 2-(*N*-formylaminomethyl)-1-nitronaphthalene (**3b**), while hydrogenated under these conditions, gave small amounts of the desired product **6b** (< 10%) and *N*-(1-aminonaphthalen-2-ylmethyl)-formamide (**8**) in *ca.* 40% yield which cyclized efficiently to **6b** only at 200 °C (EtOH, sealed tube, 10 h). Moderate amounts of the diamino derivative **5b** were also found. The collected dihydro compound **6b** underwent a spontaneous oxidation to **7b** in *ca.* 45% yield (calculated on the starting isocyanide **2b**). Additionally, the transformation of **5b** into **6b** in the reaction with triethyl orthoformate, then oxidation to **7b**, raised the overall yield to 53%. The above approach, due to the number of various operations it required, had no practical value from an experimental point of view and was not therefore applied to the synthesis of other derivatives.

The alternative pathway B was more efficient. For example, the exhaustive hydrolysis of **2b** to **4b** (concentrated HCl, MeOH–H_2O, reflux, 1 h) and subsequent hydrogenation (10% Pd–C, EtOH, 40 lbf in^{-2}, 4 h) afforded diamine **5b**, which was converted by treatment with triethyl orthoformate into the fused pyrimidine **7b** in 58% overall yield. The last step — an aromatization of the dihydro derivative (**6**) — occurred spontaneously. In addition to its simplicity, the method B allowed functionalization at C-2 by using diverse orthoesters (see compounds **7c–e**). All the synthesized products are listed in Table 1. In some cases, owing to condensation of the diamines (**5**) with two molecules of the orthoester, small quantities of the corresponding *N*-acetyl- or *N*-benzoyl-dihydropyrimidine derivatives (**9** or **10**) were formed as by-products. To avoid this side-process, the condensation with the orthoester was carried out in boiling ethanol (procedure C). Lower temperatures and dilution of the reaction mixture improved selectivity. The condensation was stopped at the stage of the dihydro compounds (**6**), giving also considerably higher yields. This procedure was demonstrated for the preparation of **6e** (84%) and **6g** (61%). The product **6e** when left at room temperature quickly started to undergo spontaneous aromatization to **7e**.



**E-mail:* Stan@ichf.edu.pl

Table 1 Fused pyrimidine derivatives

Product		Procedure	Yield (%)[a]	Mp (T/°C)[b] (solvent)
	**7a**	B	52	135–137 ($CHCl_3$)[c]
	**7b**	A	53	95–98 ($CHCl_3$–MeOH)[d]
		B	58	
	**7c**	B	44[e]	82 (subl.)
	**7d**	B	60	oil
	**7e**	B	21[f]	149–151 ($CHCl_3$)
	**6e**	C	84[g]	semi-crystalline
	**7f**	B	21	171–173 ($CHCl_3$)[h]
	**6g**	C	61	semi-crystalline

[a]Total yields based on the isocyanide (**2**). [b]Uncorrected. [c]Lit. mp 143 °C.[13] [d]Lit. mp 102–103 °C.[14] [e]Traces of **9** were found. [f]Small amount of **10** was isolated (<5% yield). [g]Small amount of **7e** was formed (6%), also product **6e** decomposed slowly to yield **7e**. [h]Lit., mp 183–184 °C.[15]

Compound **7f** exemplifies the application of the above methodology to the synthesis of purines using imidazole derivatives. Approaches to purines from imidazoles are not exhaustively described in the literature.[16] Currently we are in the midst of exploring this new type of synthetic possibility with the use of methods from our laboratory[17] and the complete results will be published soon.[18]

This work was supported by the State Committee for Scientific Research, Grant 2 P303 087 07.

Techniques used: ^{1}H NMR, MS, TLC

References: 18

Tables: 1

Schemes and Figures: 4

Received, 6th May 1997; Accepted, 25th June 1997
Paper E/7/03092D

References cited in this synopsis

1 D. J. Brown, in *The Chemistry of Heterocyclic Compounds, The Pyrimidines*, ed. E. C. Taylor, Wiley, New York, 1994.
2 (*a*) W. L. F. Armarego, in *The Chemistry of Heterocyclic Compounds, Fused Pyrimidines*, *Part I: Quinazolines*, ed. D. J. Brown, Interscience, New York, 1967; (*b*) J. H. Lister, *ibid*., *Part II: Purines*, ed. D. J. Brown, Wiley–Interscience, New York, 1971; (*c*) D. J. Brown, *ibid*., *Part III: Pteridines*, ed. E. C. Taylor, Wiley, New York, 1988; (*d*) T. J. Delia, *ibid*., *Part IV: Miscellaneous Fused Pyrimidines*, ed. E. C. Taylor, Wiley, New York, 1992.
8 Bischler's synthesis: A. Bischler, *Ber. Dtsch. Chem. Ges*., 1891, **24**, 506; W. L. F. Armarego and J. I. Smith, *J. Chem. Soc. C*, 1966, 234; Riedel's synthesis: A. Riedel, *Ger. Pat.* 174941, 1905; M. T. Bogert and E. M. McColm, *J. Am. Chem. Soc*., 1927, **49**, 2650; W. L. F. Armarego, *J. Chem. Soc*., 1962, 561; Niementowski's synthesis: S. Niementowski, *J. Prakt. Chem*., 1895, **51**(**2**), 564; ref. 2(*a*), pp. 74–78.
9 (*a*) D. Chakravarti, R. N. Chakravarti, L. A. Cohen, B. Dasgupta, S. Datta and H. K. Miller, *Tetrahedron*, 1961, **16**, 224; (*b*) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson and H. Budzikiewicz, *Tetrahedron*, 1963, **19**, 1011; (*c*) G. C. Muñoz and R. Madroñero, *Chem. Ber*., 1962, **95**, 2182.
10 (*a*) B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy and J. H. Williams, *J. Org. Chem*., 1952, **17**, 164; (*b*) N. J. Leonard and M. J. Martell Jr., *Tetrahedron Lett*., 1960, **25**, 44; (*c*) S. C. Bell and S. J. Childress, *J. Org. Chem*., 1962, **27**, 1691; (*d*) T. Goto, Y. Kishi, S. Takahashi and Y. Hirata, *Tetrahedron*, 1965, **21**, 2059.
11 (*a*) H. E. Zaugg and W. B. Martin, *Org. React*., 1965, **14**, 52; (*b*) S. Kano, Y. Tanaka, S. Sugino and S. Hibino, *Synthesis*, 1980, 695; (*c*) Y. Tomioka, K. Ohkubo and M. Yamazaki, *Chem. Pharm. Bull*., 1985, **33**, 1360.
12 M. Mąkosza, A. J. Kinowski and S. Ostrowski, *Synthesis*, 1993, 1215.
13 K. Schofield and T. Swain, *J. Chem. Soc*., 1949, 1367.
14 T. Koyama, T. Hirota, F. Yagi, S. Ohmori and M. Yamata, *Chem. Pharm. Bull*., 1975, **23**, 3151.
15 A. Bendich, P. J. Russell Jr. and J. J. Fox, *J. Am. Chem. Soc*., 1954, **76**, 6073.
16 (*a*) J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713; (*b*) A. H. Cook and E. Smith, *J. Chem. Soc*., 1949, 2329, 3001; (*c*) G. Shaw and D. N. Butler, *J. Chem. Soc*., 1959, 4040; (*d*) R. N. Naylor, G. Shaw, D. V. Wilson and D. N. Butler, *J. Chem. Soc*., 1961, 4845; (*e*) K. Kadir, G. Shaw and D. Wright, *J. Chem. Soc*., *Perkin Trans. 1*, 1980, 2728; (*f*) K. E. Andersen and E. B. Pedersen, *Liebigs Ann. Chem*., 1985, 921; (*g*) P. R. Birkett, H. King, Ch. B. Chapleo, D. F. Ewing and D. Mackenzie, *Tetrahedron*, 1993, **49**, 11029.
17 (*a*) S. Ostrowski, *Synlett*, 1995, 253; (*b*) S Ostrowski, *Heterocycles*, 1996, **43**, 389.
18 S. Ostrowski, in preparation.