JOC*Note*

Synthesis of Aminonicotinonitriles and Diaminopyridines through Base-Catalyzed Ring Transformation of 2*H*-Pyran-2-ones†

Farhanullah, Nidhi Agarwal, Atul Goel,* and Vishnu Ji Ram*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow-226001, India

vjiram@yahoo.com; agoel13@yahoo.com

Received July 8, 2002

Abstract: An efficient and convenient synthesis of 2-amino-6-aryl-4-methylsulfanylnicotinonitriles (**2**), 2-amino-6-aryl-4-substituted-aminonicotinonitriles (**4**), and 2-amino-6-aryl-4-substituted-aminopyridines (**6**) has been delineated and illustrated through base-catalyzed ring transformation of 6-aryl-3-cyano-4-methylsulfanyl/substituted-amino-2*H*-pyran-2-ones (**1**, **3**, and **5**) with cyanamide and ammonium carbonate separately.

The pyridine ring, an integral part of various natural products of therapeutic importance, plays a pivotal role in catalyzing both biological and chemical reactions. Pyridine nucleotide, the prosthetic group of many enzymes, is involved in various oxidation−reduction processes in living organisms. On the other hand, from a chemical perspective, several dialkylaminopyridines such as 4-(dimethylamino)pyridine (DMAP), 4-pyrrolidinopyridine (PPY), and their analogues have been extensively used as catalysts in acylation and alkylation[1−4] reactions as well as efficient ligands for complexation with transition metals.[5] Recently, attention has been focused to develop new catalysts for esterification of unreactive alcohols[6] and enantioselective acyl transfer.[7] Sammakia et al.[8] have developed a new strategy for the design of a catalyst that has totally separate binding and catalytic sites that offers greater flexibility and less constraint on catalytic systems. Further study revealed that the presence of certain substituents in the vicinity of the ring nitrogen of pyridine ameliorates the catalytic action.

Among various approaches to the synthesis of 4-aminopyridines, the nucleophilic substitution[9] of 4-halopyridines with amines or condensation of α,β-unsaturated carbonyl compounds with malononitriles in the presence of ammonium acetate[10] is prominent. Recently, Fort et al.[11] have described a convenient way to introduce reactive functionalities at specific positions in the pyridine ring of 4-DMAP through direct α-lithiation with BuLi−LiDMAE reagent. Though use of palladium-catalyzed amination[12,13] has been shown to be of immense value as an alternative approach for the preparation of aminopyridines, most of these procedures suffer with limitation of functional group intolerance due to harsh reaction conditions, sluggish reactions, and low yields.

Herein, we report a convenient synthesis of functionalized aminonicotinonitriles and 2,4-diaminopyridines in a single step through ring transformation of *2H*-pyran-2-ones in moderate yields. The beauty of the procedure lies in flexibility of introducing reactive functionalities at position 2, 3, 4, or 6 of the pyridine ring.

Our synthetic approach to preparing 2-amino-6-aryl-4-methylsulfanylnicotinonitriles (**2a**−**c**) is based on ring transformation of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones (**1**) by using cyanamide as a nucleophilic source. The 2*H*-pyran-2-ones (**1**) used as a parent precursor have been prepared by the reaction of methyl 2-cyano-3,3-dimethylthioacrylate with acetophenone as described earlier.[14] The lactones, 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones (**1**) on reaction with secondary amines were transformed to 6-aryl-3-cyano-4-substituted-amino-2*H*-pyran-2-ones[15,16] (**3** and **5**). The lactones **1**, **3**, and **5** were the key intermediates for the synthesis of 2-amino- and 2,4-diaminopyridine derivatives (**2**, **4**, and **6**). Thus, 2-amino-6-aryl-4-methylsulfanylnicotinonitriles (**2a**−**c**) were prepared by base-catalyzed ring transformation of **1** with cyanamide under an inert atmosphere (Scheme 1). The reaction is possibly initiated by the attack of the nucleophile ($NCNH^-$) at position C-6, a highly electrophilic site of the pyran ring due to extended conjugation and presence of an electron withdrawing substituent (CN or COOMe) at position 3, followed by the formation of a cyclic intermediate involving the nitrile functionality of cyanamide and C-3 of the pyran ring and decarboxylation to yield **2** (Scheme 1).

* To whom correspondence should be addressed. Fax: +91-522-2223405.

† CDRI Communication No. 6312.

(1) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(2) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.

(3) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129.

(4) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494.

(5) (a) Mashima, K.; Oshiki, T.; Yrata, H. *J. Organomet. Chem.* **1998**, *569*, 15. (b) Takenaka, Y.; Osakada, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 129.

(6) (a) Spivey, A.; Maddaford, A.; Fekner, T.; Redgrave, A. J.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3460. (b) Hotsuki, H.; Sakai, H.; Shinohara, T. *Synlett* **2000**, 116.

(7) (a) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234. (b) Ruble, J. C.; Twedell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794. (c) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.

(8) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, *65*, 974.

(9) Vorbrüggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117.

(10) (a) Victory, P.; Borrell, J. I.; Vidal-Ferran, A. *Heterocycl.* **1993**, *36*, 769. (b) Manna, F.; Chimenti, F.; Bolasco, A.; Bizzarri, B.; Filippelli, W.; Filippelli, A.; Gagliardi, L. *Eur. J. Med. Chem.* **1999**, *34*, 245. (c) Sakurai, A.; Midorikawa, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 430.

(11) Cuperly, D.; Gros, P.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 238.

(12) (a) Hartwig, J. F. *Synlett* **1997**, 116. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615. (d) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, *55*, 11399.

(13) (a) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J.; Putman, D. *Tetrahedron Lett.* **1998**, *39*, 1313. (b) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. (c) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (d) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568.

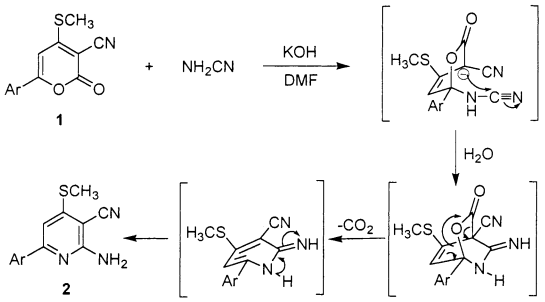
(14) (a) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y.; Kobayashi, G. *Chem. Pharm. Bull.* **1984**, *32*, 3384. (b) Tominaga, Y.; Ushirogouchi, A.; Matsuda, Y. *J. Heterocycl. Chem.* **1987**, *24*, 1557. (c) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Chem. Res. (S)*, **1991**, 98. (d) Ram, V. J.; Verma, M.; Hussaini, F. A.; Shoeb, A. *J. Liebigs. Ann. Chem.* **1991**, 1229.

(15) Ram, V. J.; Nath, M.; Srivastava, P.; Sarkhel, S.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3719.

(16) Ram, V. J.; Srivastava, P.; Agarwal, N.; Sharon, A.; Maulik, P. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1953.

10.1021/jo0204496 CCC: $25.00
Published on Web 03/11/2003

SCHEME 1



2	Ar	Yield (%)
a	C_6H_5	42
b	4-FC_6H_4	40
c	4-BrC_6H_4	38

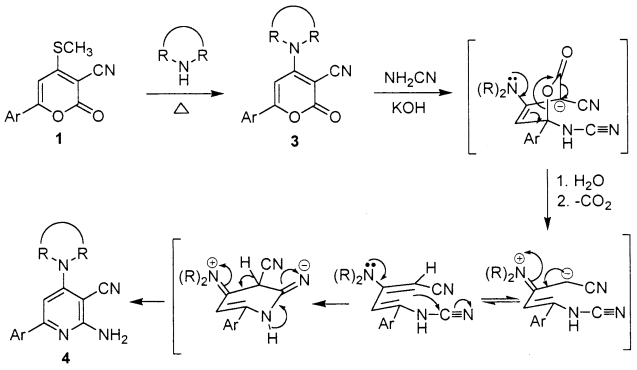
Similarly, 2-amino-6-aryl-4-substituted-aminonicotinonitriles (**4a**−**k**) were prepared in moderate yield by ring transformation of 6-aryl-3-cyano-4-substituted-amino-2*H*-pyran-2-one (**3**) by cyanamide under a nitrogen atmosphere. In this reaction, the initial step is an attack of cyanamide at position C-6 of the pyran-2-one **3**, followed by decarboxylation and ring opening. The ring-opened intermediate thus generated in situ re-cyclizes involving C-3 of the pyran ring and the nitrile functionality of cyanamide to yield **4** as shown in Scheme 2.

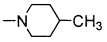
To study the effect of an electron-withdrawing CN substituent at position 3 on catalytic action of 2,4-diaminopyridine, 2-amino-6-aryl-4-substituted-aminopyridines (**6**) were synthesized through ring transformation of **5** by ammonium carbonate in pyridine at reflux temperature (Scheme 3). The plausible mechanism for the formation of **6** is possibly initiated by attack of ammonia, generated in situ from ammonium carbonate at position 6 of the pyran ring followed by decarboxylation and ring closure involving the cyano function at position 3 to yield 6-aryl-2,4-diaminopyridines (**6a**−**i**). All the synthesized compounds were characterized by spectroscopic and elemental analysis. The ^{1}H NMR of **4a** showed two sharp singlets at δ 3.26, 6.41 for dimethylamino and methine protons, respectively. A broad singlet at δ 5.16 was assigned for amino protons. The two peaks at ν 3439 and 2195 cm^{-1} in the IR spectrum revealed the presence of the amino and the cyano groups, respectively. The molecular ion peak in the mass spectrum was at *m*/*z* 238, which was in agreement with the proposed structure.

Some of the synthesized compounds (**2a**, **4a**,**b**,**d**,**f**,**g**,**i**, **6a**,**c**,**g**) were examined for their catalytic action on acetylation of *tert*-butyl alcohol with acetic anhydride as described previously,[2] but none of the compounds was found superior to DMAP.

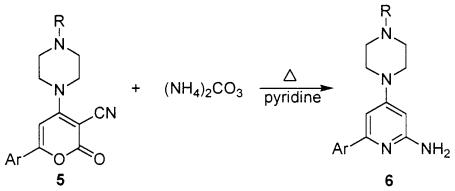
In summary, our synthetic approach is superior to the existing procedures in many ways such as (a) low-temperature reaction conditions, (b) use of inexpensive reagents, (c) versatility and compatibility of functional groups, and (d) easy workup. The synthetic strategy opens a new avenue for the synthesis of highly functionalized 2,4-diaminopyridines to develop new efficient catalysts for acylation reactions.

SCHEME 2



4	Ar	$-N\langle R \rangle R$	Yield (%)
a	C_6H_5	-$N(CH_3)_2$	51
b	C_6H_5		48
c	4-ClC_6H_4		49
d	4-BrC_6H_4	-$N(CH_3)_2$	56
e	4-BrC_6H_4		49
f	4-$CH_3C_6H_4$	-$N(CH_3)_2$	42
g	1-naphthyl	-$N(CH_3)_2$	30
h	1-naphthyl		40
i	2-naphthyl		45
j	2-naphthyl		70
k	2-naphthyl		42

SCHEME 3



6	Ar	R	Yield (%)
a	4-FC_6H_4	2-$CH_3OC_6H_4$	21
b	4-FC_6H_4	2-pyridyl	37
c	4-ClC_6H_4	2-$CH_3OC_6H_4$	43
d	4-ClC_6H_4	2-pyridyl	37
e	4-ClC_6H_4	$CH(4\text{-}FC_6H_4)_2$	43
f	4-ClC_6H_4	$CH_2C_6H_5$	35
g	4-BrC_6H_4	2-$CH_3OC_6H_4$	38
h	4-$CH_3OC_6H_4$	$CH(4\text{-}FC_6H_4)_2$	35
i	3-pyridyl	2-pyridyl	46

Experimental Section

General Procedure: Synthesis of 2-Amino-6-aryl-4-methylsulfanylnicotinonitrile (2a−c). A mixture of 6-aryl-3-cyano-4-methylsulfanyl-2*H*-pyran-2-ones (1 mmol), cyanamide (0.05 g, 1.2 mmol), and powdered KOH (0.12 g, 2 mmol) in dry

DMF (10 mL) was stirred at room temperature under inert atmosphere for 30−50 h. After completion, the reaction mixture was poured into ice−water with constant stirring and then neutralized with 10% HCl. The precipitate thus obtained was filtered and purified on silica gel column chromatography using hexane−chloroform (1:1) as eluent.

2-Amino-4-(methylsulfanyl)-6-phenylnicotinonitrile (2a): yield 42%; white solid; mp 149−150 °C; IR (KBr) 3422, 2195 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 2.62 (s, 3H), 5.21 (brs, 2H), 6.71 (s, 1H), 7.45−7.48 (m, 5H); MS *m*/*z* (FAB) 242 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.41. Found: C, 64.76; H, 4.63; N, 17.52.

Synthesis of 2-Amino-6-aryl-4-dialkylaminonicotinonitrile (4a−k). A mixture of 6-aryl-3-cyano-4-substituted-amino-2*H*-pyran-2-ones (**3**, 1 mmol), cyanamide (0.05 g, 1.2 mmol), and powdered KOH (0.12 g, 2 mmol) in dry DMF (10 mL) was stirred at room temperature under inert atmosphere for 40−50 h. After completion, the reaction mixture was poured into ice−water with constant stirring and then neutralized with 10% HCl. The precipitate thus obtained was filtered and purified on silica gel column chromatography using hexane−chloroform (1:1) as eluent.

2-Amino-4-(dimethylamino)-6-phenylnicotinonitrile (4a): yield 51%; white solid; mp 159−160 °C; IR (KBr) 3439, 2195 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 3.26 (s, 6H), 5.16 (brs, 2H), 6.41 (s, 1H), 7.41−7.52 (m, 3H), 7.82−7.89 (m, 2H); MS *m*/*z* (EI^+) 238 (M^+, 63.3). Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.5; H, 5.92; N, 23.51. Found: C, 70.58; H, 5.95; N, 23.40.

Synthesis of 6-Aryl-4-(4-aryl-1-piperazinyl)-2-pyridinamine (6a−i). A mixture of 6-aryl-3-cyano-4-substituted-amino-2*H*-pyran-2-ones (**5**, 1 mmol) and ammonium carbonate (10 mmol) in pyridine (15 mL) was refluxed for 25−35 h. After completion, the solvent was distilled off. The residue was diluted with water and extracted with chloroform. The organic layer was evaporated to dryness, and crude product obtained was purified on silica gel column using chloroform−hexane (1:1) as eluent.

6-(4-Fluorophenyl)-4-[4-(2-methoxyphenyl)-1-piperazinyl]-2-pyridinamine (6a): yield 21%; colorless oil; IR (neat) 3405 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 3.22 (t, J = 4.8 Hz, 4H), 3.64 (t, J = 4.8 Hz, 4H), 3.90 (s, 3H), 6.03 (s, 1H), 6.46 (s, 1H), 6.89 (brs, 2H), 6.93−7.20 (m, 6H), 7.71−7.86 (m, 2H); MS *m*/*z* (EI^+) 378 (M^+, 34.6). Anal. Calcd for $C_{22}H_{23}FN_4O$: C, 69.82; H, 6.13; N, 14.80. Found: C, 70.17; H, 6.21; N, 14.93.

Acknowledgment. N.A. is thankful to CSIR for the senior research fellowship.

Supporting Information Available: Characterization data (melting point, elemental analyses) and spectroscopic data (IR, ^{1}H NMR, and MS) for all the new compounds **2b**,**c**, **3b**−**k**, **4b**−**k**, **5g**−**i**, and **6b**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0204496