JOC*Note*

Synthesis of Heavily Substituted 2-Aminopyridines by Displacement of a 6-Methylsulfinyl Group

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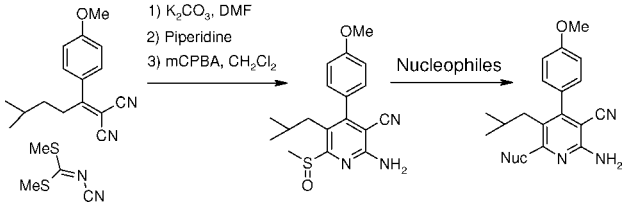
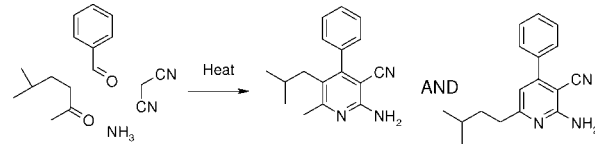


2-Aminopyridines, with a variety of polar 6-substituents, were elaborated by displacement of a methylsulfinyl group from the 6-position of the pyridine ring. The requisite 6-thiomethyl pyridines were synthesized by reaction of 2-(1-phenylethylidene)propanedinitriles with dimethyl *N*-cyanodithioiminocarbonate.

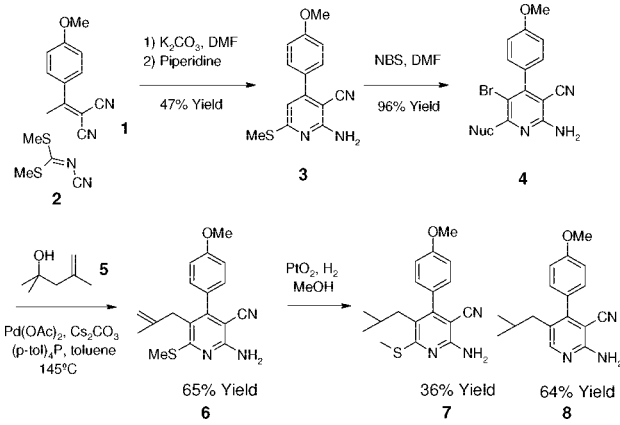
Modulation of the physical properties of unacceptably lipophilic lead molecules by introduction of polar moieties at solvent-exposed positions is a common problem for medicinal chemists. In a recent in-house study, 2-aminopyridines with polar 6-substituents were required. The scope for variation of the 4-methoxyphenyl substituent in the screening hit was limited, and the 5-isobutyl group was an absolute requirement for biological activity. This led to an intense focus upon variation of the remaining 6-substituent.

4-Aryl pyridines have diverse biological activities,[1] and a number of routes for their synthesis have been developed. Initial approaches, employing classical Hantzsch-type condensation−dehydrogenation reactions of ketones with an aryl aldehyde, malononitrile, and ammonia suffer from poor yields, regiochemical difficulties, and intolerance to polar functionality (Scheme 1). Only symmetrical, cyclic ketones perform well; unsymmetrical aliphatic ketones give much lower yields of difficult to separate regioisomers. Methyl ketones predominantly gave the 6-alkyl regioisomer, whereas for this work, the 5-alkyl isomer was required.

SCHEME 1. Classical Hantzsch Pyridine Synthesis



SCHEME 2. 6-Methylsulfinyl 2-Aminopyridine Synthesis



These difficulties were overcome by elaborating a 6-thiomethylpyridine by the unusual condensation of 2-(1-phenylethylidene)propanedinitrile (**1**) with dimethyl *N*-cyanodithioiminocarbonate (**2**) (Scheme 2).[2] Deprotonation at the γ-position of the ethylidene nitrile with potassium carbonate results in displacement of thiomethoxide from the iminocarbamate and cyclization. The resulting *N*-cyanodihydropyridine intermediate was then converted to the required aminopyridine (**3**) by addition of piperidine.

Surprisingly, the aminopyridine (**3**) could be brominated selectively, even in the presence of the electron-rich 4-(4′-methoxyphenyl) substituent, using NBS in DMF, giving the 5-bromopyridine (**4**). Negishi coupling of the aminopyridyl 5-bromide failed when the 6-position was substituted.[3] A search for such couplings where the steric demand is high suggested the use of σ-allylpalladium complexes. Heck reactions, though possible with lower alkenes, such as isobutene, are rare and experimentally challenging. This led to selection of isobutenyl transfer by in situ fragmentation of a homoallyl alcohol. The published procedure[4] was adapted to use the commercially available 2,4-dimethyl-4-pentene-2-ol (**5**) to give the 5-alkenyl pyridine (**6**). Hydrogenation of the rather hindered olefin, in the presence of a 6-thiomethyl group, proved to be possible but troublesome. A mixture of the required product (**7**) and the 6-H compound (**8**) together with starting material was isolated with all the catalysts attempted. The methane thiol, which was liberated, proved to be a very effective catalyst poison, resulting in both prolonged reaction times and heavy catalyst loadings.

Incorporating the required alkyl substituent into the initial dinitrile was attractive but unprecedented. Homologation would

(1) (a) Blonanserin: Heading, C. E. *Curr. Opin. Cent. Periph. Nerv. Syst. Invest. Drugs* **2000**, *2*, 79–84. (b) Cerivastin: Mcclellan, K. J.; Wiseman, L. R.; Mctavish, D. *Drugs* **1998**, *55*, 415–420. (c) FR 76830: Kuno, A.; Sakai, H.; Sugiyama, Y.; Takasugi, H. *Chem. Pharm. Bull.* **1993**, *41*, 156–162. (d) WIN 58161: Coughlin, S. A.; Danz, D. W.; Robinson, R. G.; Klingbeil, K. M.; Wentland, M. P.; Corbett, T. H.; Waud, W. R.; Zwelling, L. A.; Altschuler, E.; et al. *Biochem. Pharmacol.* **1995**, *50*, 111–116.

(2) Peseke, K.; Suarez, J. Q. *Z. Chem.* **1983**, *23*, 404–405.

(3) Walters, I. A. S. *Tetrahedron Lett.* **2006**, *47*, 341–344.

(4) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211.

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SCHEME 3. 5-Alkyl Aminopyridine Synthesis and Sulfinyl Displacement

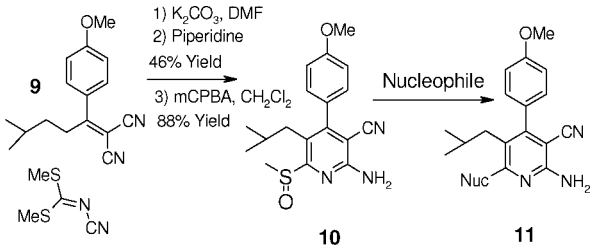
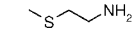
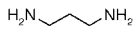
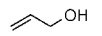


TABLE 1. Nucleophilic Displacement of the 6-Sulfinyl Group

Nucleophile	Conditions	Product (% Yield)
$MeNH_2$	25% $MeNH_2$ in MeOH 80 °C 6hrs	11a (66%)
	Neat 80 °C 6hrs	11b (65%)
	Neat 80 °C 14hrs	11c (46%)
	Neat 130 °C 72hrs	11d (14%)
	 in allyl alcohol 80 °C 36hrs	11e (41%)

be expected to affect the balance between α and γ alkylation through both steric and electronic factors.

Pleasingly, the reaction with the homologated dinitrile (**9**) preceded as required to give **7** directly (Scheme 3). Displacement of the thiomethyl group was unsuccessful. Oxidation of **7** to the sulfoxide **10** was clean with no trace of over oxidation to the sulfone even with excess oxidizing agent.

Displacement of sulfoxides from heteroaromatic and even from phenyl rings is known, though this reaction is less used than the analogous displacement of sulfones.[5] Functionalized primary amines were conveniently introduced by heating the sulfoxide with the nucleophile to give compounds **11a**−**e** (Table 1). Secondary amines were slow to displace the methylsulfinyl group and produced a mixture of the required product **11d** and the thiomethyl pyridine (**7**) through concomitant deoxygenation of the sulfoxide. Displacement with alcohols, which are much less nucleophilic than amines, required deprotonation and prolonged heating giving **11e**.

The route made possible the synthesis of compounds with aqueous solubility suitable for biological evaluation. However, the localization of all polarity into only a small fraction of the molecule is suboptimal, producing amphipathic molecules which disrupt cellular systems nonselectively.

(5) On pyridines: (a) Hirokawa, Y.; Horikawa, T.; Kato, S. *Chem. Pharm. Bull* **2000**, *48*, 1847–1853. (b) Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem Soc., Perkin Trans. 1* **1984**, *8*, 1839–1845. On quinolines: (c) Maslankiewicz, M. J.; Maslankiewicz, A. *Heterocycles* **2007**, *71*, 175–180. On a phenyl: (d) Clayden, J.; Stimson, C. C.; Keenan, M. *Chem. Commun.* **2006**, *13*, 1393–1394. Reviewed: (e) Furukawa, N. *Sulf. Rep.* **1986**, *7*, 47–88.

Experimental Section

Compound 7. 2-Amino-4-(4-methoxyphenyl)-5-(2-methylpropyl)-6-(methylsulfanyl)pyridine-3-carbonitrile. Potassium carbonate (0.20 g, 1.45mmol) was added in one portion to a stirring solution of 2-(1-(4-methoxyphenyl)-4-methylpentylidene)propanedinitrile (0.32 g, 1.26 mmol) and dimethyl *N*-cyanodithioiminocarbonate (0.18 g, 2.19 mmol) in DMF (5 mL) at ambient temperature. The resulting heterogeneous solution was stirred at ambient temperature for 18 h. Piperidine (0.2 mL, 2.02 mmol) was added, and the reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dried over sodium sulfate, filtered, and evaporated to afford crude product. The crude solid was triturated with ethanol and isolated by filtration. Drying under vacuum gave the product as an off white solid (0.19 g, 0.56 mmol, 46%): ^{1}H NMR ($CDCl_3$) δ 7.15 (d, 2H), 6.97 (d, 2H), 5.01 (s, 2H), 3.84 (s, 3H), 2.51 (s, 3H), 2.2 (d, 2H), 1.8 (m, 1H), 0.64 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 165.7, 160.8, 158.1, 153.4, 131.2, 130.00, 124.2, 118.5, 115.00, 88.6, 56.3, 37.7, 29.0, 23.5, 14.9; exact mass MH^+ 328.1487; formula $C_{18}H_{22}N_3OS$ requires MH^+ 328.1484; deviation 0.3 ppm; HPLC purity 91.4%.

Compound 10. 2-Amino-4-(4-methoxyphenyl)-5-(2-methylpropyl)-6-(methylsulfinyl)pyridine-3-carbonitrile. Sulfide (0.120 g, 0.35 mmol) in dichloromethane (10 mL) was treated with *m*-chloroperbenzoic acid (0.1 g, ∼70%, 0.41 mmol). The reaction was instantaneous. Ethyl acetate (40 mL) was added to the reaction mixture, which was then washed with saturated aqueous sodium bicarbonate. The organic extract was dried over magnesium sulfate and evaporated. The residue was triturated with ether giving a white solid (0.11 g, 0.31 mmol, 88%): ^{1}H NMR ($CDCl_3$) δ 7.2 (br d, 2H), 6.99 (br d, 2H), 5.32 (s, 2H), 3.82 (s, 3H), 2.82 (s, 3H), 2.8−2.6 (m, 2H), 1.4 (m, 1H), 0.67 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 163.9, 160.3, 158.2, 157.3, 130.0, 129.7, 127.5, 124.1, 115.5, 114.3, 95.9, 55.3, 39.2, 35.1, 30.6, 22.2, 21.8; exact mass MH^+ 328.1487; formula $C_{18}H_{22}N_3O_2S$ requires MH^+ 344.1483; deviation 0.4 ppm; HPLC purity 86.6%.

Compound 11b. 2-Amino-4-(4-methoxyphenyl)-6-(methylamino)-5-(2-methylpropyl)pyridine-3-carbonitrile. Sulfoxide (10 mg, 0.028 mmol) was heated to 80 °C in a sealed vial with methylamine in methanol (1 mL, ∼25%) for 6 h. The reaction mixture was evaporated and columned in ethyl acetate/isohexane (1:1) to give a white solid (6 mg, 0.018 mmol, 66%): ^{1}H NMR ($CDCl_3$) δ 7.18 (d, 2H), 6.96 (d, 2H), 4.88 (s, 2H), 4.79 (s, H), 3.92 (s, 3H), 3.02 (d, 3H), 2.18 (dd, 2H), 1.5 (m, 1H), 0.66 (dd, 6H); ^{13}C NMR ($CDCl_3$) δ 159.3, 158.7, 158.6, 152.4, 130.1, 129.9, 119.0, 113.7, 109.2, 79.4, 55.2, 35.2, 28.7, 27.3, 22.6; exact mass MH^+ 311.1885; formula $C_{18}H_{23}N_4O$ requires MH^+ 311.1872; deviation 1.3 ppm; HPLC purity 97.5%.

Acknowledgment. This work is dedicated to Prof. A. I. Meyers. His love of creativity in heterocyclic chemistry has been an enduring inspiration. His guidance, group members, and location of work is a memory held dear.

Supporting Information Available: Experimental procedures and analytical data for compounds **3**, **4**, **6**, **7**, **8**, **9**, **10**, and **11a**−**e** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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