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Technical Notes

Practical Amination of Nitropyridones by Silylation

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Abstract:

A practical method for coupling nitropyridones (1) with primary amines by treatment with hexamethyldisilazane has been developed, avoiding the use of hazardous reagents such as $POCl_3$. The activation of the pyridone by a nitro group is necessary for efficient coupling, leading to aminonitropyridines (3) in good yields. Regioisomers other than 3-nitro-4-pyridone (1) were found to be substantially less reactive but would undergo coupling with primary amines.

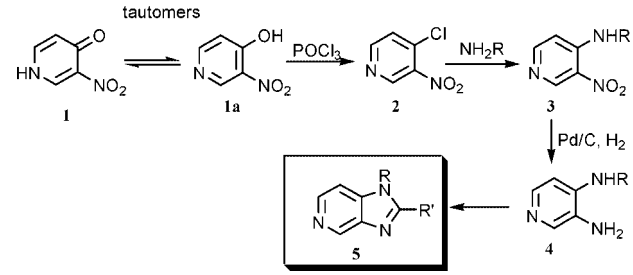
Introduction

During our process research and development work on potential drug candidates in early development, we encountered the need to prepare various aminonitropyridines (**3**) as precursors for azabenzimidazoles (**5**). Originally we used a conventional approach to prepare this family of compounds by displacement of a chloronitropyridine (**2**) with the appropriate primary alkylamine (Scheme 1).[1] The chloronitropyridine was prepared from the corresponding nitropyridone (**1**) with $POCl_3$.[1,2] Since **2** and some chloronitropyridine derivatives are irritants and potential sensitizers,[3] we elected to utilize more benign starting materials that would be sufficiently activated to undergo substitution. Herein we describe the process research and development of a safer activation of nitropyridones to enable coupling with primary amines.

Results and Discussion

Aside from the conversion of **1** to a halide such as **2**, other conventional approaches to the activation of nitropyridone (**1**) include the formation of the sulfonate[4] or phosphonium salts.[5] While these options were likely to be viable, they still utilized hazardous or toxic reagents. As another option, we were intrigued by reports in the literature[2,6] that methoxynitropyridines had demonstrated the ability to undergo substitution with primary amines. We explored the viability of this substrate class

Scheme 1. **General route to azabenzimidazoles (5) via 4-amino-3-nitropyridine (3)**



and found that primary amines coupled readily with **1b** in isopropanol under ambient conditions to furnish **3a**−**d** in good isolated yields (Table 1). Upon reaction completion, the products crystallized following addition of water to the reaction mixture. While this was a viable process alternative to using the corresponding chloronitropyridine, the desired methoxynitropyridines were not as readily available nor as inexpensive as the corresponding hydroxy-substituted derivatives.[7]

In order to avoid the use of $POCl_3$[8] and a separate activation step of the nitropyridones, we explored the use of hexamethyldisilazane (HMDS). We speculated that HMDS could be sufficient to carry out in situ activation

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(1) Crey-Desiolles, C.; Kotera, M. *Bioorg. Med. Chem.* **2006**, *14*, 1935–1941.

(2) Provencal, D. P.; Gesenberg, K. D.; Wang, H.; Escobar, C.; Wong, H.; Brown, M. A.; Staab, A. J.; Pendri, Y. R. *Org. Process Res. Dev.* **2004**, *8*, 903–908.

(3) Material Safety Data Sheets on 2-chloro-3-nitropyridine and 4-chloro-3-nitropyridine indicate that these materials are severe irritants and that the 2-chloro isomer is a skin sensitizer.

(4) (a) Mugnaini, C.; Petricci, E.; Botta, M.; Corelli, F.; Mastromarino, P.; Giorgi, G. *Eur. J. Med. Chem.* **2007**, *42*, 256–262. (b) Cain, G. A.; Beck, J. P. *Heterocycles* **2001**, *55*, 439–446. (c) Zhao, H.; Serby, M. D.; Xin, Z.; Szczepankiewicz, B. G.; Liu, M.; Kosogof, C.; Liu, B.; Nelson, L. T. J.; Johnson, E. F.; Wang, S.; Pederson, T.; Gum, R. J.; Clampit, J. E.; Haasch, D. L.; Abad-Zapatero, C.; Fry, E. H.; Rondinone, C.; Trevillyan, J. M.; Sham, H. L.; Liu, G. *J. Med. Chem.* **2006**, *49*, 4455–4458.

(5) Phosphonium salts have often been formed with reagents such as BOP, see: (a) Kang, F.-A.; Kodah, J.; Guan, Q.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957–1960. (b) Wan, Z.-K.; Binnum, E.; Wilson, D. P.; Lee, J. *Org. Lett.* **2005**, *7*, 5877–5880. (c) Wan, Z.-K.; Wacharasindhu, S.; Binnum, E.; Mansour, T. *Org. Lett.* **2006**, *8*, 2425–2428.

(6) (a) Bamford, M. J.; Alberti, M. J.; Bailey, N.; Davies, S.; Dean, D. K.; Gaiba, A.; Garland, S.; Harling, J. D.; Jung, D. K.; Panchal, T. A.; Parr, C. A.; Steadman, J. G.; Takle, A. K.; Townsend, J. T.; Wilson, D. M.; Witherington, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3402–3406. (b) Lanza, T. J.; Durette, P. L.; Rollins, T.; Siciliano, S.; Cianciarulo, D. N.; Kobayashi, S. V.; Caldwell, C. G.; Springer, M. S.; Hagmann, W. K. *J. Med. Chem.* **1992**, *35*, 252–258.

(7) The price of 4-methoxy-3-nitropyridine is about $5/g to $20/g in cost (depending on the choice of supplier) while the corresponding hydroxypyridine is about $1/g to $4/g. In addition we had issues with the quality of 4-methoxy-3-nitropyridine; one supplier provided samples contaminated with up to 50% of *N*-methyl-3-nitro-4-pyridone.

(8) $POCl_3$ can be hazardous for both laboratory use and the environment, see: (a) Kapias, T.; Griffiths, R. F. *J. Hazard. Mater.* **2001**, *81*, 223–249.

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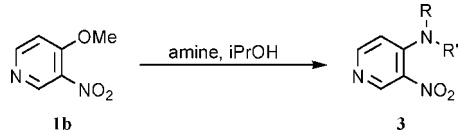
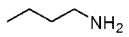
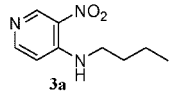
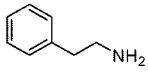
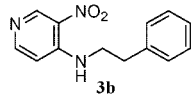
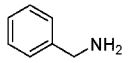
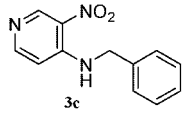
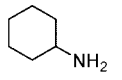
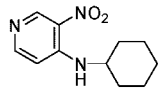
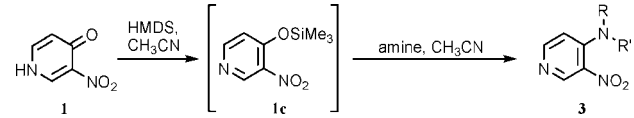
Table 1. **Addition of amines to 1b**[a]

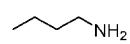
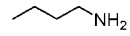
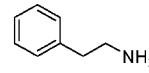
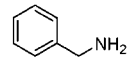
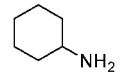
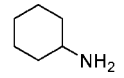


Entry	Amine	Product	Time	Yield[b]
1		 **3a**	6 h	92%
2		 **3b**	8 h	91%
3		 **3c**	24 h	89%
4		 **3d**	24 h	90%

[a] Reaction conditions: Used 1 equiv of **1b**, 2.0 equiv of amine, ambient conditions in isopropanol (1.5 M relative to **1b**). [b] Isolated yield.

Table 2. **Addition of amines to 3-nitro-4-pyridone (1)**[a]



Entry	Amine	Product	Time	Yield[b]
1		**3a**	8 h	90%
2		**3a**	24 h	65%[c]
3		**3b**	12 h	91%
4		**3c**	24 h	92%
5		**3d**	36 h	82%[d]
6		**3d**	24 h	NR[d,c]

[a] Reaction conditions: Used 1 equiv of **1**, 1.5 equiv of HMDS, 2.0 equiv of amine in CH_3CN (4 mL/g **1**) at 60 °C. [b] Isolated yield. [c] Reaction carried out in DMAC. [d] Reaction carried out at 75 °C.

of the hydroxypyridine tautomer (**1a**) by silylation to enable substitution by primary amines. A benefit of using HMDS was that the silylating reagent would not react with the amine to be coupled nor with the nitrogen of the pyridine ring,[9] and could also serve to remove water from the system through formation of siloxane byproduct. Others have reported the use of HMDS for activating heterocycles, such as pyridines, toward amination reactions, but high temperatures and Lewis acids were typically required since the systems studied were not activated with electron-withdrawing groups.[10] We were pleased to find that we could adapt this in situ activation to a practical protocol that could be readily implemented on a kilogram scale. It was unnecessary to execute the process in a stepwise manner; rather, the amine (2.0 equiv) and HMDS (1.5 equiv) were combined with 3-nitro-4-pyridone (**1**) in acetonitrile and heated to 60 °C for 8−24 h. Upon reaction completion, the reaction mixture was concentrated to remove solvent and siloxane byproduct. The products were typically crystallized from the crude reaction mixture. The polarity of the reaction solvent seemed to play a critical role since no reaction was observed in THF, dichloromethane, or acetone. While DMF or DMAC could be used, the reactions were slower,[11] and dimethylamine adducts formed in DMF as a result of decomposition to dimethylamine during heating.[12] In addition, acetonitrile possessed the advantage of enabling solvent removal by distillation to facilitate workup and isolation. The order of addition of HMDS and the amine had no impact on the rate of the reactions, demonstrating that HMDS does not interact with the amine. We also observed no difference in relative rates whether using 1 equiv or 3 equiv of HMDS. This suggests that the main role of HMDS is silylation of the hydroxyl group and additional activation by silylation of the nitro group is unlikely.[13] For examining the reaction scope, 3-nitro-4-pyridone (**1**) was coupled with various primary amines in a tandem process (Table 2).

The preparation of benzimidazole **5a** was demonstrated on a kilogram scale.[14] We decreased the charge of propylamine to 1.5 equiv and lowered the reaction temperature due to the volatility of propylamine. We also noticed with optimization of the reaction that fewer polar side products formed with a lower loading of propylamine. The addition was complete within 48 h by using 1.5 equiv of HMDS in acetonitrile with 1.5 equiv of propylamine at 45 °C. After crystallization from 10:1 water/acetonitrile, the product was isolated in 82% yield. The product was then reduced under hydrogenation conditions in THF (8 mL/g) and crystallized from toluene to afford diamine **4a** as white crystals in 78% yield. To complete the preparation of benzimidazole **5a**, diamine **4a** was dissolved in isopropylacetate (20 mL/g of **4a**) and treated with 4 equiv of chloroacetic anhydride under ambient conditions (Scheme 2). The acylation proceeded rapidly, but the ring closure required stirring for several hours. The excess anhydride

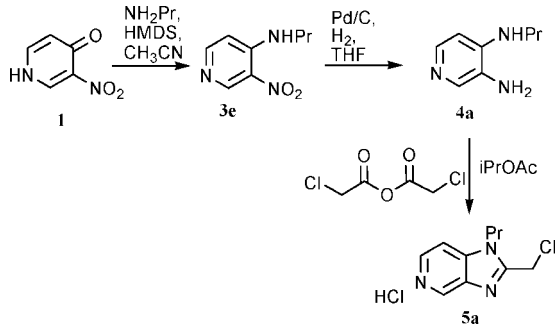
(9) Due to the high affinity of silicon to oxygen, silylation always occurs on oxygen rather than nitrogen, see: (a) Vorbruggen, H.; Krolikiewicz, K. *Liebigs Ann. Chem.* **1976**, 745–761. (b) Vorbruggen, H.; Krolikiewicz, K.; Niedballa, U. *Liebigs Ann. Chem.* **1975**, 988–1002. (c) Cook, M. J.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem.* **1974**, *17*, 255–356.

(10) HMDS has been used in the past to activate hydroxy pyridines toward substitution by amines, see: (a) Vorbruggen, H.; Krolikiewicz, K. *Chem. Ber.* **1984**, *117*, 1523–1541. (b) Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 305–306.

(11) Polar solvents generally are favored for aromatic substitution reactions which most likely progress through a charged intermediate such as a Meisenheimer salt, see: (a) Meisenheimer, J. *Liebigs Ann. Chem.* **1902**, *323*, 205–246. (b) Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* **1983**, *34*, 305–444. (c) Brewis, D. M.; Chapman, N. B.; Paine, J. S.; Shorter, J.; Wright, D. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, *15*, 1787–801.

(12) The decomposition of DMF to dimethylamine and CO is well-known, see: (a) Neumeyer, J. L.; Cannon, J. G. *J. Org. Chem.* **1961**, *26*, 4681–4682.

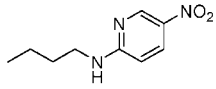
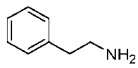
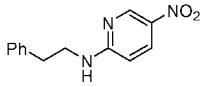
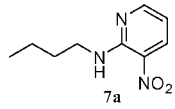
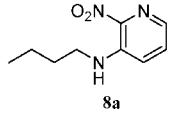
Scheme 2. **Processing route to benzimidazole 5a**



initially allowed formation of a diacylated intermediate which then would undergo ring closure. The acylation and ring closure tolerated heating up to 40 °C, but higher temperatures (60−70 °C) resulted in increased levels of side products generally arising from alkylation at the α-chloride. Maintaining a pH in the range of 3−6 was essential for efficient ring closure following the acylation. For this reason the anhydride was optimal for targeting the desired pH range; however, the corresponding acid chloride, chloroacetyl chloride, was ineffective in the cyclization unless the reaction was buffered with pyridine or other mild bases. Once complete, the reaction was worked up with base, and the product (**5a**) was crystallized as the HCl salt from isopropanol in 67% yield.

Other regioisomers of nitropyridone, 5-nitro-2-pyridone (**6**), 3-nitro-2-pyridone (**7**), and 3-hydroxy-2-nitropyridine (**8**), were evaluated and were found to be much less reactive than **1** as substrates (Table 3). These results illustrate the sensitivity of the electrophile to electronic effects.

Table 3. **Addition of amines to 5-nitro-2-pyridone (6), 3-nitro-2-pyridone (7), or 3-hydroxy-2-nitropyridine (8)[a]**

Entry	Amine	Product	Time	Yield[b]
1		 **6a**	48 h	44%
2		 **6b**	24 h	7%[a]
3		 **7a**	48 h	61%
4		 **8a**	48 h	8%[a]

[a] Reaction conditions: Used 1.0 equiv of nitropyridone, 2.0 of equiv amine, 75 °C, CH_3CN (4 mL/g nitropyridone). [b] Isolated yield. [c] Product not isolated.

(13) Silylation of nitro groups to facilitate nucleophilic aromatic substitution has been observed, see: Makosza, M.; Surowiec, M. *Tetrahedron* **2003**, *59*, 6261–6266.

(14) We had tested compound **5a** as a potential mutagen and found that it was negative in the Sprial Ames test as well as in the in Vitro Micronucleus test.

Conclusion

In summary, we have developed a practical one-pot procedure for silylating nitropyridones and coupling with primary amines which was demonstrated on a kilogram scale. From our survey in this area there are some clear limitations on the class of substrates viable for utilizing this methodology; however, the highly activated nitropyridones appear to readily undergo amination. Regioisomers other than 3-nitro-4-pyridone were found to be substantially less reactive. This technology is well suited for the preparation of azabenzimidazoles which typically utilize primary amine additions to activated nitropyridines. Finally, this methodology also possesses the advantage of avoiding hazardous reagents such as $POCl_3$ which are often used for the activation of heterocycles to undergo additions by amines.

Experimental Section

General Procedure for Amination of Nitropyridones. To a suspension of the nitropyridone (5.00 g, 35.7 mmol) in acetonitrile (20 mL), was added HMDS (11.3 mL, 53.5 mmol) and the mixture was stirred for 15 min. The amine (71.4 mmol) was added and the resulting mixture was heated at 60 °C for 16 h. Acetonitrile was removed under reduced pressure, and isopropanol (10 mL) was added and then concentrated. The crude material was purified by crystallization. Isopropanol (10 mL) was added, and the mixture was cooled at 0 °C and stirred for 5 min. Water (75 mL) or isopropyl ether (75 mL) was added dropwise, and the crystals formed were stirred at 0 °C for 3 h. The crystals were filtered, washed with either water (15 mL) or isopropyl ether (15 mL), and dried affording the pure aminonitropyridine as crystals.

Preparation of 3e on Kilogram Scale. To a suspension of the nitropyridone (5.5 kg, 39.3 mol) in acetonitrile (22 L), was added HMDS (12.4 L, 59.0 mol), and the mixture was stirred for 15 min. Then propylamine (3.50 kg, 59.2 mol) was added, and the resulting mixture was heated at 45 °C for 48 h. Isopropanol (10 L) was charged, and the reaction mixture was concentrated in vacuo to remove excess HMDS. This was solvent exchanged for acetonitrile, and the volume was adjusted to ∼12 L. Water (75 L) was added to crystallize the product. After 3 h of stirring, the crystals were filtered and washed with water to remove residual acetonitrile. The product was dried at 45 °C to yield yellow-green crystals (5.85 kg, 82%). Mp = 65−66 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.36 (s, 1H), 8.20 (d, J = 6.0 Hz, 1H), 6.95 (d, J = 6.0 Hz, 1H), 3.32 (dt, J = 13.5, 6.0 Hz, 2H), 1.52−1.61 (m, 2H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.3, 149.0, 148.8, 129.8, 109.2, 44.2, 22.1, 11.7; Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.10; H, 6.15; N, 23.22.

Preparation of Diamine 4a by Hydrogenation. To a solution of **3e** (5.4 kg, 29.8 mol, 1.0 equiv) in THF (43 L) was added 10% palladium on carbon (180 g, 50% wet by weight). The Hastelloy vessel was sealed, charged with nitrogen, and pressurized to 50 psi of hydrogen. After 2 h of stirring, the reaction was filtered through a pad of Celite (pad washed with THF). The filtrate was concentrated in vacuo and displaced with toluene. The product diamine was recrystallized by heating in

toluene (24 L) to afford white crystals (needles). These were filtered and dried under vacuum at 50 °C to obtain **4a** (3.5 kg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 5.3 Hz, 1H), 7.85 (s, 1H), 6.45 (d, J = 5.3 Hz, 1H), 4.22 (s, 1H), 3.11 (dd, J = 6.0 Hz, 2H), 2.43 (s, 2H), 1.62−1.71 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 144.1, 138.0, 128.6, 105.0, 45.0, 22.6, 11.8.

Preparation of Benzimidazole 5a. To a solution of chloroacetic anhydride (15 kg, 4.0 equiv) in isopropyl acetate (197 L) was added **4a** (3.3 kg, 21.8 mol, 1.0 equiv) under ambient conditions. After stirring for 18 h at 20−25 °C, the reaction mixture was washed once with a 5.0 M aqueous solution of NaOH (50 L), then once with a 1.0 M aqueous solution of NaOH (33 L), and once with a saturated aqueous solution of NaCl (33 L). The organic layer was concentrated to about half of the batch volume. In a separate vessel acetyl chloride (2.22 kg, 1.3 equiv) was added to isopropanol (50 L) to make anhydrous HCl. The solution of crude product in isopropyl acetate was slowly added to the solution of anhydrous HCl in isopropanol to precipitate the product. The product formed a white precipitate and was stirred for 3 h under ambient conditions. The crystals were filtered, washed with isopropanol, and dried at 50 °C to produce white crystals of **5a** (3.6 kg, 67%) as an HCl salt. ^{1}H NMR (400 MHz, CD_3OD) δ 9.34 (s, 1H), 8.61 (d, J = 6.6 Hz, 1H), 8.32 (d, J = 6.6 Hz, 1H), 5.13 (s, 2H), 4.51 (t, J = 7.5 Hz, 2H), 2.00 (sxt, J = 7.5 Hz, 2H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 158.4, 145.9, 139.2, 135.1, 133.9, 109.7, 46.9, 35.3, 22.9, 10.2.

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Supporting Information Available

Experimental procedures, characterization data and ^{1}H NMR and ^{13}C NMR spectra for products **3a**−**d**, **6a**, and **7a** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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