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LETTERS

Reductive decyanation of pyrazinecarbonitriles

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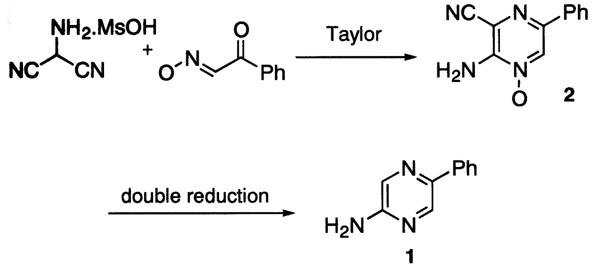
Abstract—Pyrazinecarbonitriles can be decyanated by hydrogenation with platinum on carbon in the presence of activated carbon under acidic conditions. Pyrazine carbonitrile-*N*-oxides undergo a stepwise reduction to the deoxy-pyrazinecarbonitriles followed by decyanation to give pyrazines in good yields. © 2002 Published by Elsevier Science Ltd.

Pyrazine derivatives are naturally occurring and important pharmaceutical intermediates, which have been used in the synthesis of pterins, pteridines, quinoxalines, nucleosides, polymers, antioxidants, pesticides, antiviral and cytotoxic agents.[1]

We recently required kilogram quantities of 2-amino-5-phenylpyrazine **1**, and so we sought an efficient and economical synthesis of this intermediate. Starting from readily available, inexpensive starting materials we have developed an operationally simple process that relies on formation of the pyrazine by a Taylor condensation[1a] followed by a double reduction (Scheme 1).

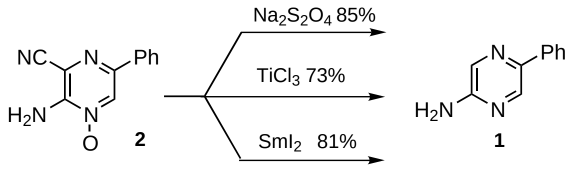


Scheme 1.

The Taylor condensation is an attractive method to generate 2-amino-pyrazine-*N*-oxides with varying functionality in the five and six positions. The conditions are very mild and the yields are typically very good. In our hands, the condensation reaction of aminomalononitrile methanesulfonate salt[2] and isonitrosoacetophenone in methanol occurred at room temperature (Scheme 1).[3] The product crystallized out of solution as the reaction progressed. Isolation by filtration provided the desired product **2** in 92% yield and >99% purity.

While there are many methods to reduce *N*-oxides, decyanation reactions are relatively rare.[4] We did not pursue the transformation of the nitrile into the carboxylic acid, as it is well known that decarboxylation of pyrazinecarboxylic acids can be very difficult and intolerant of many functional groups.[5]

Several reductants were screened for their ability to both reduce the *N*-oxide and remove the nitrile under mild conditions. Initially sodium dithionite was used to effect the double reduction (Scheme 2).[6] Despite extensive optimization, the reaction was not entirely reliable. Also, the volume productivity was relatively low and not amenable to scale-up. Titanium trichloride is known to effect decyanation of 4-cyanopyridine,[7] and did indeed cause decyanation of **2** to give **1** in 73% yield, but with several side products. Four equivalents of samarium diiodide effected a much cleaner decyanation reaction to produce **1** in 81% yield. While the price of samarium has decreased in recent years, it is still too expensive for scale-up.



Scheme 2.

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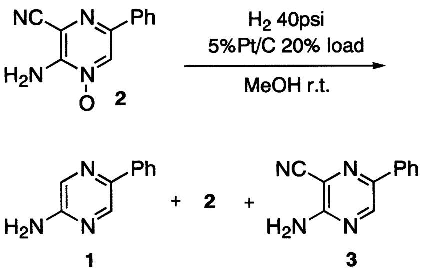
Hydrogenation on Pt/C with 20% catalyst loading returned a mixture of **1** plus **2** plus the deoxy-intermediate **3** (Scheme 3). Increasing the catalyst load to 100% returned the doubly reduced **1** in 90% yield. We reasoned that prevention of catalyst poisoning would allow the reaction to proceed to completion with a reasonable catalyst loading. Experimentation with various additives such as strongly cyanide-chelating transition metal salts (e.g. $ZnCl_2$) failed to prevent poisoning of the catalyst, and in fact slowed the reaction down appreciably. The addition of 3 Å sieves made little difference to the reaction, but the addition of activated carbon Norit RO allowed the reaction to progress to 70% completion with 25% catalyst load. Screening of activated carbon products revealed that Darco KB-B gave the highest and most consistent yields for this reaction and allowed us to decrease the platinum catalyst load to only 10%.



Scheme 3.

The addition of acids was also examined. Addition of sulfuric acid led to over-reduction of the pyrazine ring. Addition of glacial acetic acid enhanced the rate of reaction without over-reduction problems. Decyanation is much slower with Pd/C catalyst compared to Pt/C, and deoxy-product **3** was isolated as the major product. No reaction occurred in the absence of hydrogen gas, even at elevated temperatures, which tends to rule out an organometallic insertion process.[8] Solvent, temperature and pressure were also optimized (Scheme 4).

Deuterium labeling studies were performed. In all experiments, deuterium incorporation was found at the C-3 position of the pyrazine ring, replacing the cyano group, and in no other positions (Fig. 1).

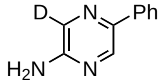


Figure 1.

To explore the generality of this mild decyanation reaction, several pyrazine substrates were synthesized and subjected to the optimized conditions (Table 1).[9] Compound **2** was *N*-acylated and subjected to the decyanation conditions: acylation of the amine (entry 2) does not hinder the reaction. The amino group is not necessary to direct the reaction: the parent compound cyanopyrazine (entry 4) was transformed into pyrazine in 78% yield. The camphor-derived pyrazine-*N*-oxide (entry 6) did not eliminate cyanide under our optimized conditions—or at elevated temperature and pressure and 30% catalyst loading. Only the deoxygenated product was isolated. It may be that this substrate is unable to adhere to the catalyst due to the steric hindrance of the camphor methyl groups. The decyanation is specific to pyrazines: 2-cyanopyrimidine and cyanopyridines are inert (Fig. 2). A dicyanoimidazole was also subjected to these conditions, and found to be inert as well.

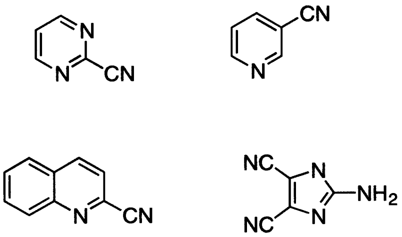
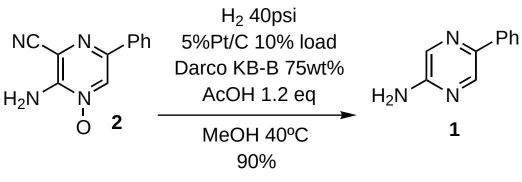


Figure 2.

In summary, we have developed a mild and robust protocol for the deoxygenation/decyanation of pyrazines. We have demonstrated that the decyanation is a general reaction for pyrazines, and a selective reaction over other heterocycles.

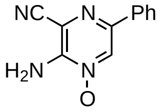
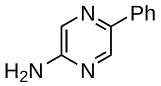
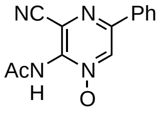
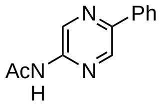
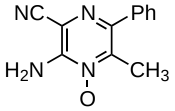
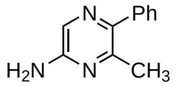
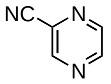
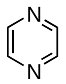
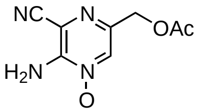
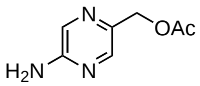
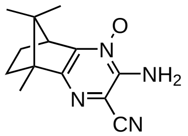
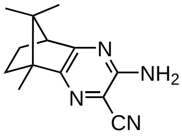
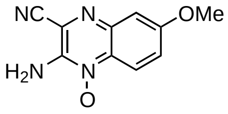
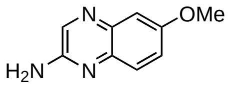


Scheme 4.

Acknowledgements

We thank Andrew Newell, Charles Bazaral and Tony Houck for their expertise with high pressure equipment. We thank Tony King, Cecile Savarin and Spencer Dreher for helpful suggestions.

Table 1.

Entry	R-CN	Product	Yield
1			92%
2			87%
3			73%
4			78%
5			99%
6			90%[a]
7			89%

[a] Yield of deoxy product - no decyanation occurred.

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2. For preparation of aminomalononitrile methanesulfonate salt, see: Mettler, H. US 482015, our improved procedure follows: (1) A solution of $NaNO_2$ (2.17 kg in 5.0 L H_2O) was prepared. A slurry of malononitrile (**1**) (1.98 kg, 30.0 mol) in water (5.0 L) was cooled to 15°C, then $NaNO_2$ solution (0.8 L, ~15% of the total) was added followed by H_2SO_4 (5N, 0.60 L, 10 mol%). The pH of the mixture should be 3.0–3.5. The remaining $NaNO_2$ solution was added slowly (1–2 h) with ice-water bath to control the batch at 15–20°C. The mixture was then aged at 15–20°C for 1 h. Final pH should be 4.0–4.2. Sulfuric acid (5N, 5.70 L) was added to acidify the reaction mixture to pH ~2.0 at 15–20°C. The oxime is unstable in acidic aqueous solution and should be kept <20°C. The mixture was extracted with EtOAc (15 L, then 5 L). The combined batch was washed with brine (7.5 L) then submitted to hydrogenation. (2) HOAc (7.5 L) was added to the crude solution of oxime (~23 L). Pt/C (5%, 0.57 kg) was added and the mixture was hydrogenated at 10 bar H_2 for 20 h at 10–15°C. The mixture was filtered through a Solka-Floc

pad and rinsed with 10 L of EtOAc. Methanesulfonic acid (3.17 kg, 2.14 L) was added over 2 h with a dropping funnel at 10–15°C. The mixture was aged for 1 h then filtered to collect the product, which was dried under a stream of nitrogen to constant weight to give the mesylate salt as a white crystalline solid (4.78 kg, 90% yield).

3. To a solution of isonitrosoacetophenone (1.69 kg, 10 mol, 88% pure) in methanol (15 L) and water (0.4 L) was added in portions the mesylate salt (1.95 kg) over 5 h at rt to give a very thick slurry. The product crystallizes as the mesylate salt is added and the reaction proceeds. The mixture was aged overnight and then quenched with a solution of Na_2CO_3 (0.87 kg in 8 L water). The pH of the quenched mixture was 8–9. The product was collected by filtration and washed with 1/1 $MeOH/H_2O$ (8 L) and dried by passing air through the filter cake to constant weight, to give the product as an fluffy bright yellow solid, 1.934 kg, 99 w%, 90% corrected yield.
4. Alshaar, A. H. M.; Chambers, R. K.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc*., *Perkin Trans. 1* **1992**, 2789–2811.
5. Sarma, M. S. P.; Czarnick, A. W. *Synthesis* **1988**, 72–73.
6. Sodium dithionite is unstable at elevated temperatures and under acidic conditions. By using a mixture of sodium dithionite 3 equiv. and sodium carbonate 1 equiv., the reaction gave 70–75% isolated yield. Unfortunately, about 50 volumes are required.
7. Clerici, A.; Porta, O. *Tetrahedron Lett*. **1980**, *21*, 1675–1676.
8. For a rare example of C–CN bond activation by a nickel complex which promotes cross coupling, see: Miller, J. A. *Tetrahedron Lett*. **2001**, *42*, 6991–6993.
9. Experimental for decyanation reaction: A slurry of pyrazine *N*-oxide **2** (2.00 g, 9.4 mmol), 5% Pt/C (0.30 g, 15% catalyst loading), Darco KB-B (1.50 g, 75% loading) and glacial acetic acid (0.650 mL, 11.3 mmol) in methanol (40 mL) was submitted for hydrogenation at 40 psi and 40°C for 18 h in pressure apparatus. After hydrogen atmosphere was flushed with nitrogen, a solution of sodium hydroxide (0.450 g, 11.3 mmol) in 2 mL water was added. The reaction mixture was filtered through Solka-Floc to remove catalyst. Solka Floc/catalyst was rinsed with 1 L methanol. *Caution! the filtrate contains the majority of cyanide as NaCN!* The filtrate was concentrated to ~5–6 mL by rotary evaporator *in a fume hood*. Water (10 mL) was added. Aged for 1 h. The precipitate was collected by filtration and air-dried overnight in hood to give pale yellow solids 1.47 g, 91% yield.