

Catalytic hydrogenation of ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate and its Schiff base reaction modes

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Abstract—Under heterogeneous catalysis, ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate or its Schiff base could be selectively reduced in good yield by hydrogenation to give a diamine, or to form a five-membered ring or a six-membered ring heterocycles. This selectivity is highly dependent on the type of catalysts used.

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Eflornithine or α -difluoromethylornithine (DFMO) is marketed as a therapeutic treatment for African sleeping sickness and for the removal of unwanted facial hair in women. During our investigation of a practical and scalable synthesis, the efficient reduction of an aminonitrile **1** to diamine **2** in the presence of an ester group within the molecule was required. In the literature, a nitrile group could be reduced to a primary amine by hydrogenation using catalysts¹ such as Pd/C, Pt/C, PtO₂, Raney Ni or Co, or homogeneous Rh catalysis,² by borane,³ metal boron hydrides⁴ or lithium aluminium hydride⁵ with or without catalyst. However, some of these methods were not suitable for this chemical transformation due to side reactions or difficulties in isolation. Hydrogenation under heterogeneous catalysis appeared most applicable and was investigated using our substrate with multifunctional groups, ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate or its Schiff base. Here, we wish to report our results.

Ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate is readily prepared from benzophenone Schiff base of glycine ethyl ester via alkylation with 3-bromopropionitrile or Michael addition with acrylonitrile,⁶ followed by a second alkylation with chlorodifluoromethane⁷ then hydrolysis with dilute hydrochloric acid.

Ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate was initially subjected to hydrogenation under the catalysis of 5% Pd/C in MTBE or ethyl alcohol with 3–4 equiv of concd HCl. However, less than 5% of the desired diamine hydrochloride salt was obtained due to intramolecular cyclization reaction to give **3**. It has been reported that under hydrogenation conditions aminonitrile or cyano esters could undergo intramolecular cyclization reaction to give a pyrrolidine (amino group reacts with a cyano group) or a piperidone (amine group reacts with an ester group).⁸ However, there has been no systematic study on the effect of catalysts on the reduction of aminonitrile esters. Interestingly, we found that the selectivity of reactions was highly dependent on the type of catalysts used. Selected results are summarized in Table 1.

Several commercially available catalysts were screened. It can be seen from the table that under Pd/C catalysis (entries 1 and 2), hydrogenation gave the desired diamine salt with <5% selectivity. A cyclized product, a proline derivative was obtained as the major product, indicating that intramolecular cyclization is faster than reduction of the newly formed imine (intermediate of nitrile reduction). While using Pt/C as catalyst under similar conditions, the reaction gave predominantly the desired diamine compound in a selectivity of 71–82% (entries 5–8) with an average isolated yield of 72.4%. PtO₂ showed similar selectivity and Rh/C showed decreased selectivity with the diamine and the cyclized product in a ratio of 2:3, but Ru/C gave multiple products (entries 3, 4 and 13). Sources (from different vendors) of Pt/C appeared to have little impact

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Table 1. Transition metal-catalyzed hydrogenation of aminonitriles⁹

Entry	R	Reaction conditions				Selectivity (%)	
		Solvent	Catalyst	Time (h)	Pressure	Diamine	Cyclized
1	H	MTBE	5% Pd/C	24	120 psi	2	98
2	H	MTBE	5% Pd/C	17	130	5	95
3	H	MTBE	5% Rh/C	19	120	41	59
4	H	MTBE	5% Ru/C	17	130	—	—
5	H	MTBE	5% Pt/C (DeGussa)	21	130	74	26
6	H	MTBE	10% Pt/C (Aldrich)	21	130	78	22
7	H	MTBE	5% Pt/C (Engelhard)	18	120	71	29
8	H	MTBE	Pt/C	17	120	80	20
9	H	Ethanol	Pt/C	63	120	71	29
10	H	IPA	Pt/C	19	110	77	23
11	H	THF	Pt/C	22	112	81	19
12	H	CH ₂ Cl ₂	Pt/C	22	112	—	—
13	H	MTBE	PtO ₂	19	110	75	25
14	R ₂ = Ph ₂ C	MTBE	10 Pt/C (Aldrich)	16	125	82	18
15	R ₂ = Ph ₂ C	MTBE	10% Pt/C (Engelhard)	4	125/45 °C	76	24
16	R ₂ = Ph ₂ C	AcOH	10 Pt/C (Aldrich)	4	125	76	24
17 ^a	R ₂ = Ph ₂ C	EtOH	Raney Co (Engelhard)	2	125	>99	<1

^a Five grams of the catalyst was loaded for per gram of substrate.

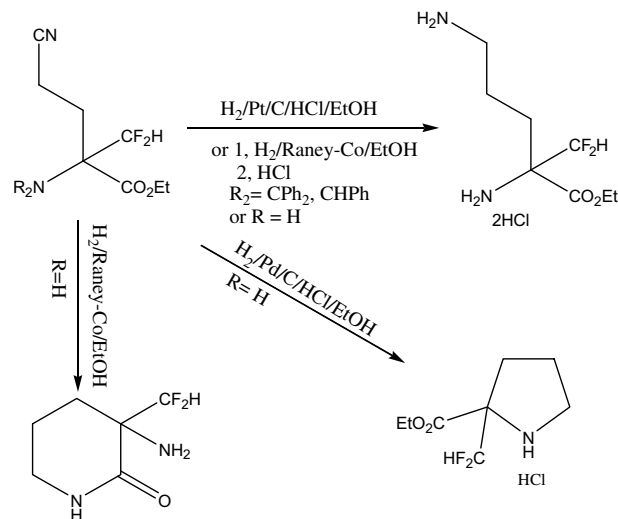
on selectivity (entries 5–7). Ethers or alcohols seemed to be better solvents for this reaction than an aprotic solvent, such as methylene chloride, due to the low solubility of starting material under acidic conditions (entries 8–12).

To simplify the process, the Schiff base of ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate was directly used without hydrolysis prior to hydrogenation. Similar selectivity and yields were obtained (entries 14–16). The selectivity for diamine formation could significantly be improved when the benzophenone Schiff base was subjected to hydrogenation using Raney Co in ethyl alcohol under neutral conditions (entry 17). Although the reaction required high catalyst loading at 2–5 g/g, it reduced completely the cyano group to the amine group without affecting the Schiff base double bond. The resulting product was found unstable and degraded slowly due to a side reaction. However, the desired diamine could be isolated by forming the hydrochloride salt upon hydrolysis of the Schiff base immediately after reduction. This gave exclusively the desired diamine **2** in >99% selectivity and ~85% isolated yield. Raney Ni, however, gave inferior results under similar conditions.

Interestingly, under the catalysis of Raney Co hydrogenation of ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate in the absence of hydrochloric acid afforded exclusively a piperidone derivative, implying that the nitrile reduction is faster than intramolecular reaction of the amino group and the imino group during hydroge-

nation. This piperidone compound could also be hydrolyzed to give DFMO.

In conclusion, we have discovered that ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate and its Schiff base are useful intermediates for preparing DFMO and are versatile precursors to three types of compounds under various catalytic conditions. The three reaction modes are depicted in Scheme 1.

**Scheme 1.**

Supplementary data

Supplementary data associated with this article can be found, in the online version at [doi:10.1016/j.tetlet.2005.02.146](https://doi.org/10.1016/j.tetlet.2005.02.146).

References and notes

- (a) Secrist, J. A.; Logue, M. *J. Org. Chem.* **1972**, *37*, 335; (b) Shih, T. L.; Ruiz-Sanchez, J.; Mrozik, H. *Tetrahedron Lett.* **1987**, *28*, 6015; (c) Gould, F. E.; Johnson, G. S.; Ferris, A. F. *J. Org. Chem.* **1960**, *25*, 1658; (d) Staskun, B.; Es, T. V. *J. Chem. Soc. (C)* **1966**, 531; For reviews, see: (e) Freifelder, M. In *Practical Catalytic Hydrogenation*; Wiley Interscience: New York, 1971, pp 238–260; (f) Freifelder, M. In *Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary*; J. Wiley and Sons: New York, 1978; pp 43–52; (g) Rylander, P. N. In *Hydrogenation Method*; Academic: New York, 1985; pp 94–103, pp 94–103.
- Yoshida, T.; Okano, T.; Otsuka, S. *J. Chem. Soc., Chem. Commun.* **1979**, 870.
- (a) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1960**, *82*, 681; (b) Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1986**, *51*, 4856; (c) Brown, H. C.; Choi, Y. M.; Nagasimhan, S. *Synthesis* **1981**, 605; (d) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.
- (a) Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000; (b) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 2582; (c) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555; (d) Haizman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801; (e) Osby, J. O.; Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67.
- (a) Nystrom, R. F.; Brown, W. *J. Am. Chem. Soc.* **1948**, *70*, 3738; (b) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544; (c) Cimino, G.; Gavagnin, M.; Sodano, G.; Schmitz, F.; Yalamanchili, G. *J. Org. Chem.* **1987**, *52*, 2301; (d) Takada, S.; Makisumi, S. *Chem. Pharm. Bull.* **1984**, *32*, 873; (e) Frejd, T.; Klingsted, T. *Synthesis* **1987**, 40.
- (a) Zhang, F.-Y.; Corey, E. *J. Org. Lett.* **2000**, *2*, 1097; (b) Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* **1999**, *10*, 713; (c) O'Donnell, M. J.; Bennett, W. D.; Bruder, W. A.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520; For review: (d) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3.
- (a) Bey, P.; Vevert, J.-P.; Dorsselaer, V.; Kolb, M. *J. Org. Chem.* **1979**, *44*, 2732; (b) Bey, P.; Schirlin, D. *Tetrahedron Lett.* **1978**(52), 5225.
- (a) Welsh, W. M. *J. Org. Chem.* **1982**, *47*, 886; (b) Demopoulos, B. J.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.* **1983**, *61*, 2415.
- A typical procedure for hydrogenation: To a 460 mL hastelloy bomb is added 10% Pt–C (2.2 g) and EtOH (30 mL). The contents are agitated and pressurized under hydrogen (95 psi) for 1 h. To the vessel is then added concentrated HCl (20.8 g, 4 equiv) and **1a** (20 g), as a solution in EtOH (170 mL). The contents are repressurized and agitated (500 rpm) until the starting material disappears. The reaction mix is filtered over Celite and the pad washed with 2 × 20 mL EtOH. The filtrate is then concentrated under vacuum at 40 °C while EtOH (310 mL) is added to compensate for volume loss. Distillation continues until the final mass is ~80 g. MTBE (120 mL) is then added over 10 min at 40 °C to facilitate crystallization of **2**. After cooling to room temperature, the slurry is agitated for 1 h, filtered over a Buchner funnel, and the cake was washed with 2 × 20 mL MTBE. After being pulled dry, the crude weight is 11.65 g (76.2% yield).