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Chemoselective Reduction of Highly-functionalized Azidopyridazines to Corresponding Aminopyridazines Using Fe/NH_4Cl in Organic Solvent-Water Two-phase Solution

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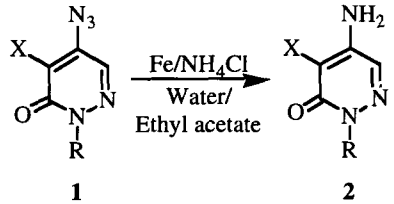
Abstract; Highly functionalized azidopyridazines can be reduced chemoselectively to the corresponding amines in excellent yields.

The reduction of azides to amines is a synthetically important process and its value has been well established.[1] Of the convenient methods available for the conversion of azides to amines, the most popular involve catalytic hydrogenation,[2] Staudinger condition,[3] hydrogen sulfide,[4] thiol under basic condition,[5] metal hydride,[6] and tetrathiomolybdate.[7] Most of these methods, however, often suffer from one or more limitations with respect to general applicability, selectivity, ready availability, operational convenience.[6c] Fe/NH_4Cl in a mixed solution of ethyl acetate and water has been used for reducing nitroarenes,[8] but little attention has been focused on reduction of azides under this condition. During the course of our synthetic study on diazine-fused nitrogen-heterocycles,[9] we found that azidopyridazines substituted by various types of functional groups can be reduced chemoselectively and efficiently to the corresponding amines under this condition.



1 **2**

Table 1.

Entry.	X	R	yield (%)[a]	mp (°C)[b]
a	Cl	CH_2COCH_3	93	194-195
b	Br	CH_2COCH_3	95	192-193
c	Cl	CH_2COOCH_3	97	222-223
d	Br	$CH_2C(=NOH)CH_3$	92	204-205
e	Br	CH_2CH_2CN	98	219-220
f	Cl	$CH_2C[O(CH_2)_2O]CH_3$	97	229-230
g	Cl	$CH_2(CH_2)_3O$-COC_6H_5	96	137-138

[a]Purified yields. [b]Uncorrected.

The results are summarized in Table 1. Azidopyridazines **1** bearing various functional groups[10] were simply stirred with the excess amount of Fe powder (3 equiv.) and NH4Cl (5 equiv.) in the two phase solution of ethyl acetate and water at room temperature to give amines **2** in excellent yields. Amines **2**[11] were purified as free amines by filtering the Fe powder, evaporating the organic phase, and recrystallizing or chromatographing the crude products. The reactions described here proceed in chemoselective fashion, keeping a variety of functional groups such as halogen, carbonyl, nitrile, oxime, ester, acetal and acyloxy, intact and complete within 2 hr at room temperature. The reactions can also be performed using other common organic phase such as benzene, chloroform or methanol in place of ethyl acetate to give the products in comparative yields. The present α–amino-β–halopyridazines **2** should find their way as useful synthons for the construction of a variety of fused nitrogen-heterocycles by a^2, d^o / a^n, d^o combination.[12]

This idea and the expanded results of this novel method to other heterocyclic azides will be published elsewhere.

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10. The starting azides used were prepared by nucleophilic displacement using sodium azide and the corresponding halides. The details with respect to the preparation of starting azides will be published elsewhere.
11. For **2a**; white needles; IR (KBr) 3460, 3344, 3226(NH_2), 1744(C=O), 1660(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 2.10(s, 3H), 4.80(s, 2H), 6.77(br. s, NH_2), 7.56(s, 1H) ppm; ^{13}C NMR (DMSO-d_6) 26.9, 60.1, 79.0, 130.0, 145.6, 156.9, 201.7 ppm; MS m/z (%) : 201 (10, M^+), 159 (23, M^+-42), 131 (7, M^+-70), 32 (100, M^+-169) : **2b**; white needles; IR (KBr) 3456, 3292, 3178(NH_2), 1734(C=O), 1632(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 2.12(s, 3H), 4.83(s, 2H), 6.80(br. s, NH_2), 7.54(s, 1H) ppm; ^{13}C NMR (DMSO-d_6) 26.6, 60.2, 79.7, 129.8, 149.6, 157.3, 202.2 ppm; MS m/z (%) : 246 (14, M^+), 203 (37, M^+-43), 175 (10, M^+-71), 68 (48, M^+-178), 43 (100, M^+-203) : **2c**; white needles; IR (KBr) 3436, 3332, 3218(NH_2), 1754(C=O), 1658(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 3.66(s, 3H), 4.75(s, 2H), 6.88(br. s, NH_2), 7.62(s, 1H) ppm; ^{13}C NMR (DMSO-d_6) 51.9, 52.5, 79.0, 130.2, 145.7, 156.9, 168.2 ppm; MS m/z (%) : 217 (43, M^+), 185 (25, M^+-32), 158 (74, M^+-59), 32 (100, M^+-185) : **2d** ; white needles; IR (KBr) 3444, 3322, 3200, (NH_2), 1648(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 1.67 & 2.14(s, 3H, syn & anti), 4.65 & 4.85(s, 2H, syn & anti), 6.75 & 6.80(s, NH_2, syn & anti), 7.52(s, 1H), 10.71(s, OH) ppm; ^{13}C NMR (DMSO-d_6) 11.6, 26.9, 53.7, 60.3, 79.0, 129.4, 129.5, 147.2, 147.5, 150.9, 157.1 ppm; MS m/z (%) : 261 (48, M^+), 246 (64, M^+-15), 203 (64, M^+-58), 122 (57, M^+-139), 95(58, M^+-166), 68(65, M^+-193), 40(100, M^+-221) : **2e**; white needles; IR (KBr) 3462, 3364, 3242(NH_2), 2250(CN), 1646(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 2.93(t, 2H), 4.20(t, 2H), 6.84(br. s, NH_2), 7.56(s, 1H) ppm; ^{13}C NMR (DMSO-d_6) 16.2, 46.4, 79.0, 118.2, 129.7, 147.4, 156.9 ppm; MS m/z (%) : 242 (40, M^+), 204(27, M^+-38), 189 (72, M^+-53), 132 (29, M^+-110), 32 (100, M^+-210), 40 (100, M^+-203) : **2f**; white needles; IR (KBr) 3422, 3326, 3208(NH_2), 1658(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 1.25(s, 3H), 3.88(m, 4H), 4.06(s, 2H), 6.77(br. s, NH_2), 7.58(s, 1H) ppm; ^{13}C NMR (DMSO-d_6) 23.0, 53.7, 64.1, 107.5, 129.4, 145.1, 157.2 ppm; Anal. Calcd. for $C_9H_{12}N_3O_3Cl$: C, 44.0; H, 4.92; N, 17.10. Found: C, 43.90 H, 4.79 N, 17.18 : **2g**; pale yellow needles; IR (KBr) 3502, 3320, 3204(NH_2), 1740(C=O), 1658(C=O) cm^{-1}; ^1H NMR (DMSO-d_6) 1.75(m, 4H), 4.03(t, 2H), 4.27(t, 2H), 6.73(br. s, NH_2), 7.49-7.96(m, 6H) ppm; ^{13}C NMR (DMSO-d_6) 24.6, 25.2, 49.9, 64.1, 128.5, 128.9, 129.5, 129.7, 133.0, 145.2, 156.9, 165.6 ppm; Anal. Calcd. for $C_{15}H_{16}N_3O_3Cl$: C, 55.99; H, 5.01; N, 13.06. Found: C, 56.15 H, 4.91 N, 13.24
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