

SYNTHESIS OF α -AMINO KETONE HYDROCHLORIDES VIA
 CHEMOSELECTIVE HYDROGENATION OF α -NITRO KETONES

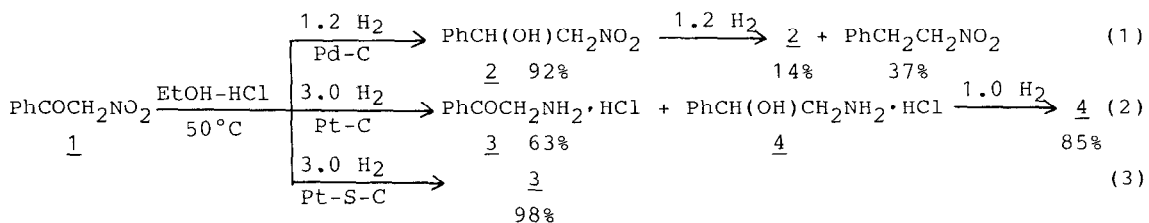
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Summary: Chemoselective hydrogenation of various α -nitro ketones was accomplished with 5% Pt sulfide on carbon as a catalyst to afford α -amino ketone hydrochlorides in good yields.

Synthesis of a variety of α -nitro ketones has been easily accomplished by the choice of appropriate synthetic procedures: (i) acylation of primary nitroalkanes,¹ (ii) nitration of cyclic enol esters and enol silyl ethers,² and (iii) classical oxidation of β -nitro alcohols.³ Along with their ready accessibility, new synthetic reactions utilizing α -nitro ketones have recently been devised.⁴ To our knowledge, there has been no example for selective conversion of α -nitro ketones to α -amino ketone hydrochlorides,^{5,6} which are known to be valuable precursors for asymmetric synthesis of β -amino alcohols⁷ and for synthesis of symmetric and unsymmetric pyrazines.⁸ Here we wish to report a new and convenient method to prepare α -amino ketone hydrochlorides via chemoselective hydrogenation of α -nitro ketones catalyzed by 5% platinum sulfide on carbon (Pt-S-C).^{9,10}

Initially α -nitroacetophenone (1) was subjected to hydrogenation conditions (1 atm. of H₂, 50°C) with 5% Pd-C catalyst in ethanol-conc.HCl (20:1 V/V). After absorption of 1.2 mole equiv of H₂, undesired β -nitro alcohol 2 was obtained in 92% yield, and further reaction resulted in hydrogenolysis of 2 to give β -nitroethylbenzene (eq 1). Switching the catalyst to 5% Pt-C afforded α -amino ketone hydrochloride 3 in 63% yield with the formation of β -amino alcohol hydrochloride 4 after absorption of 3.0 mole equiv of H₂ (eq 2). This indicated that 3 underwent further reduction during hydrogenation of 1 with 5% Pt-C and that the catalyst should be properly deactivated to give 3 selectively. Thus, the use of a Pt catalyst deactivated



by a sulfur compound (5% Pt-S-C) completely suppressed the formation of 4 and gave 3 chemoselectively and quantitatively (eq 3).¹¹

The above difference of chemoselectivity between Pd and Pt catalysts was well interpreted in terms of (i) the strong affinity of Pd to π -electrons of benzene ring resulting in the reduction of the neighboring carbonyl group, and (ii) the relatively high adsorption activity of Pt to the negatively charged oxygen of the nitro group.¹²

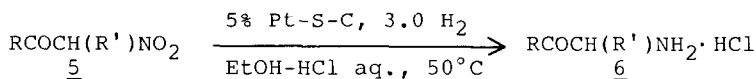
Using 5% Pt-S-C, chemoselective hydrogenation of various α -nitro ketones was attempted. The results are shown in the Table. Reduction of aryl nitro-methyl ketones shows the outstanding electronic effect of substituents. As the para substituent on benzene ring changes from an electron-withdrawing group to an electron-donating group, the reaction rate decreases (Cl>H>>Me>OMe, entries 1 through 4), reflecting the electrophilic character of the α -nitro ketones. Despite the reaction rates, after absorption of 3.0 mole equiv of H₂ the desired products are obtained in good yields. In contrast, reduction of aryl α -nitroalkyl ketones is severely susceptible to the steric hindrance in the nitroalkyl group, i.e., in the hydrogenation of α -nitropropionophenone, the carbonyl group is hydrogenated in place of the nitro group, even though Pt-S-C is the catalyst, giving the corresponding β -nitro alcohol in 62% yield (entry 6).¹³

Although the choice of the proper metal catalyst is not critical in the hydrogenation of alkyl α -nitroalkyl ketones due to the absence of an aryl group attached to the carbonyl group, 5% Pt-S-C is a more suitable catalyst than 5% Pd-C in yield. As shown in entries 7 through 10, this system is not very sensitive to steric inhibition, and α -amino ketone hydrochlorides are selectively obtained in good yields.

A typical experimental procedure for conversion of 5 to 6 is as follows. α -Nitroacetophenone (1) (0.83 g, 5.0 mmol), dissolved in ethanol (20 mL) containing conc. HCl (1 mL), was hydrogenated with 5% Pt-S-C (0.1 g) at 50°C (1 atm.). Three mole equiv of H₂ was absorbed in 2 hr, at which time hydrogen uptake practically ceased. The catalyst was removed by filtration and washed with methanol (10 mL). The filtrate was evaporated under reduced pressure. Acetone (10 mL) was added to the resulting residue to precipitate the hydrochloride salt. The solvent was removed by filtration and the white salt was washed with acetone (10 mL). Removal of the solvent in vacuo gave analytically pure α -aminoacetophenone hydrochloride (3), 0.84 g (98% yield).

By taking advantage of chemoselective hydrogenation of α -nitro ketones described above, synthesis of terephthaloylbis(methylamine) dihydrochloride (7), a compound which is expected as a building block for the preparation of aromatic oligomers, was achieved starting from terephthaloylchloride as depicted in Scheme. Terephthaloyldiimidazole, prepared by Staab's method,¹⁴ was transformed into terephthaloylbis(nitromethane) in 75% yield, and subsequently hydrogenated with 5% Pt-S-C to give 7 in 92% yield.

Thus, α -amino ketone hydrochlorides are obtainable under mild hydrogenation conditions from various α -nitro ketones for which synthetic methods have been well established.

Table. Hydrogenation of α -Nitro Ketones with 5% Pt-S-C^a

entry	R	R'	time, h ^b	<u>6</u> ^c , isolated yield, %
1	4-Cl-C ₆ H ₄	H	1	85
2	Ph	H	2	98
3	4-Me-C ₆ H ₄	H	11.5	85
4	4-MeO-C ₆ H ₄	H	22.5	73
5	2-Naphthyl	H	14	85
6	Ph	Me	14	-- ^d
7	Et	H	9	84 (76) ^e
8	Me ₂ CHCH ₂	H	15	66 (46) ^e
9	-(CH ₂) ₄		6	61
10	Me	Me	6	85

a) Reactions were performed on 5.0 mmol scale using 0.1 g of 5% Pt-S-C.

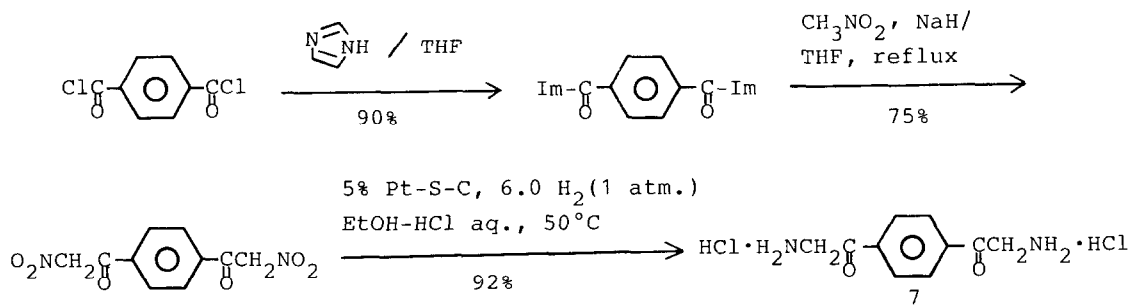
b) Time required for absorption of 3.0 mole equiv of H₂.

c) All products were fully characterized by means of infrared, ¹H NMR spectra, and elemental analyses.

d) PhCH(OH)CH(Me)NO₂ was obtained in 62% yield.

e) 5% Pd-C was employed in place of 5% Pt-S-C.

Scheme



References and Notes

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 - 5) Direct conversion of aliphatic α -nitro ketones to pyrazines and piperazines with catalysts such as Pt oxide, Raney Ni, and Pd-C under ca. 3-32 atm. of hydrogen was reported: A. F. Ellis, U. S. Pat. 3,453,278 [C. A., 71, 91526f (1969)].
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 - 9) Five % Pt-S-C is commercially available from Engelhard Industries, INC.
 - 10) A nitro group is reduced to an amino group with uptake of 3 mole equiv of H₂ via nitroso (= oxime) and hydroxylamine intermediates.
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(Received in Japan 19 August 1986)