

A GENERAL PROCEDURE FOR MILD AND RAPID REDUCTION OF ALIPHATIC AND AROMATIC NITRO COMPOUNDS
USING AMMONIUM FORMATE AS A CATALYTIC HYDROGEN TRANSFER AGENT

Siya Ram and Richard E. Ehrenkauf*
Cyclotron/PET Facility, Division of Nuclear Medicine
The University of Michigan Medical School, Ann Arbor, Michigan 48109

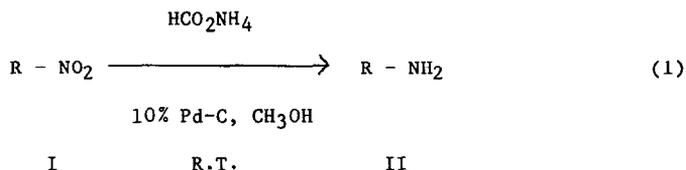
ABSTRACT

Various aliphatic and aromatic nitro compounds were selectively and rapidly reduced to their corresponding amino derivatives in very good yield using anhydrous ammonium formate as a catalytic hydrogen transfer agent.

Selective and rapid reduction of nitro compounds is still an area of considerable synthetic interest¹, particularly when a molecule has several other reducible moieties. Numerous new reagents²⁻¹⁴ have been developed for reduction of aromatic nitro compounds, however little attention has been paid to the reduction of aliphatic nitro compounds^{4,7,8}, which are traditionally reduced by high pressure catalytic hydrogenation^{15,16}. In the past 30 years catalytic transfer hydrogenation¹⁷⁻²² has demonstrated great potential value in organic and biological chemistry. Cyclohexene/Pd-C has been most widely studied. Recently, ammonium formate has been successfully employed as a catalytic hydrogen transfer agent in peptide chemistry for deprotection²³⁻²⁴ instead of cyclohexene. Reduction of azides²⁵ and cyano groups²⁶ to the corresponding amines and methyl group has also been reported in the recent literature.

In our ongoing program, we were interested in the radioisotopic synthesis of ¹¹C-amino acids (¹¹C-half life = 20.4 min) via nitro acid intermediates. We have thus examined several classes of chemical reducing agents for e.g. FeSO₄/NH₄OH, Cyclohexene/Pd-C, NH₂-NH₂/Ra-Ni, Zn/AcOH, etc., however these systems failed to yield the amino acid. In this paper we wish to report a mild, simple, rapid and selective reduction of aliphatic and aromatic nitro compounds to the corresponding amino derivatives using ammonium formate (Scheme-I).

SCHEME I



R = alkyl or aryl

A typical experimental procedure for conversion of I to II is as follows.

TABLE I. Reduction of aliphatic and aromatic nitro compounds to corresponding amines.

No.	Nitro Compound	Reaction time in min.	Product ^b	Yield ^a %
1	CH ₃ CH ₂ CH ₂ NO ₂	< 30	CH ₃ CH ₂ CH ₂ NH ₂ ·HCl	31 ^c
2	CH ₃ CH ₂ CH ₂ CH ₂ NO ₂	< 20	CH ₃ CH ₂ CH ₂ CH ₂ NH ₂ ·HCl	49 ^c
3	(CH ₃) ₂ CHCH ₂ CH ₂ NO ₂	< 40	(CH ₃) ₂ CHCH ₂ CH ₂ NH ₂ ·HCl	82
4	C ₂ H ₅ O ₂ CCH ₂ NO ₂	20	C ₂ H ₅ O ₂ CCH ₂ NH ₂ ·HCl	64
5	HOOC(CH ₂) ₂ NO ₂	20	⁻ OOC(CH ₂) ₂ NH ₃ ⁺	98
6	CH ₃ O ₂ C(CH ₂) ₃ NO ₂	20	CH ₃ O ₂ C(CH ₂) ₃ NH ₂	81
7	CH ₃ O ₂ CCH ₂ CH ₂ CH(CH ₃)NO ₂	15	CH ₃ O ₂ CCH ₂ CH ₂ CH(CH ₃)NH ₂ and 5-methyl-2-pyrrolidinone	75
8	p-O ₂ NC ₆ H ₄ CO ₂ H	5-10	p-H ₂ NC ₆ H ₄ CO ₂ H	52 ^d
9	4-H ₃ COC ₆ H ₃ (3-NO ₂)CO ₂ H	5-10	4-H ₃ COC ₆ H ₃ (3-NH ₂)CO ₂ H	75 ^d
10	p-O ₂ NC ₆ H ₄ CH ₂ CO ₂ H	5-10	p-H ₂ NC ₆ H ₄ CH ₂ CO ₂ H	86
11	p-O ₂ NC ₆ H ₄ CO ₂ CH ₃	5-10	p-H ₂ NC ₆ H ₄ CO ₂ CH ₃	89
12	C ₆ H ₅ NO ₂	3-5	C ₆ H ₅ NH ₂	76
13	o-FC ₆ H ₄ NO ₂	3-5	o-FC ₆ H ₄ NH ₂	70
14	p-H ₃ COC ₆ H ₄ NO ₂	3-5	p-H ₃ COC ₆ H ₄ NH ₂	93
15	4-H ₃ CC ₆ H ₃ (2-NO ₂)NH ₂	3-5	3,4-(NH ₂) ₂ C ₆ H ₄ CH ₃	79
16	p-O ₂ NC ₆ H ₄ CH ₂ C≡N	120	p-H ₂ NC ₆ H ₄ CH ₂ C≡N	85
17	2-H ₂ NC ₆ H ₃ (5-NO ₂)COC ₆ H ₅	15	2,5-(NH ₂) ₂ C ₆ H ₃ COC ₆ H ₅	91
18	m-O ₂ NC ₆ H ₄ CH ₂ NHC(=NH)NH ₂	25	m-H ₂ NC ₆ H ₄ CH ₂ NHC(=NH)NH ₂	70
19	2-I-C ₆ H ₃ (4-NO ₂)CONH ₂	60	p-H ₂ NC ₆ H ₄ CONH ₂	31 ^e
20	2-H ₃ C-5-NO ₂ -imidazole	Partial reduction, with rapid product decomposition.		

(a) Isolated yields are based on the single experiment and yields were not optimized;

(b) Products were characterized by comparison with authentic samples (IR, ¹H-NMR, TLC and m.p.);

(c) The low yields of aliphatic amines are due to low boiling points (n-propylamine b.p. 48°, n-butylamine b.p. 78°) and their volatile nature;

(d) These were obtained by trituration with small amount of water, the low yield in the case of p-aminobenzoic acid is due to its partial solubility in water. Modified workup is required for such water soluble products;

(e) No reaction takes place using Pd-C as the catalyst. When Raney-Nickel is used the resulting product is the deiodinated amine, p-aminobenzamide.

To a stirred suspension of an appropriate nitro compound (5 mmol) and 10% Pd-C (0.2 - 0.3 g) in dry methanol (10 mL), anhydrous ammonium formate was added (23 mmol) in a single portion. The resulting reaction mixture (slightly exothermic and effervescent) was stirred at room temperature for 3-40 min under argon, the catalyst was removed by filtration through a celite pad and washed with dry methanol (10 mL). The filtrate was evaporated either under reduced or at normal pressure. The resulting residue was triturated with water (10 mL - 25 mL), product was extracted with an organic solvent (i.e. ether, CH₂Cl₂ or CHCl₃) and dried over Na₂SO₄. The organic layer on evaporation gave the desired amino derivative. Some products were directly converted into the HCl-salt with ethereal-HCl without evaporation of ether layer.

The scope of this new general procedure is shown in Table I. In most cases the reaction is over within 3-40 min, however for p-nitrobenzyl cyanide 16, the reaction completion time was 120 min. In cases of iodinated aromatic systems, 2-iodo-4-nitrobenzamide 19 and 1-iodo-3-nitrobenzene no reaction was observed, however using Raney-Nickel as catalyst with 19, reduction of the nitro group as well as deiodination occurred, yielding p-aminobenzamide. These observations suggest that iodinated compounds may deactivate the Pd-C catalyst.

m-Nitrobenzylguanidine 18, which was unable to be reduced to the corresponding m-amino-benzylguanidine in the variety of conditions²⁷, was successfully reduced by 10% Pd-C/HCO₂NH₄ - CH₃OH system in 70% yield. Although methyl-4-nitropentanoate 7 was successfully reduced to corresponding amino acid ester, partial cyclization also occurred yielding 5-methyl-2-pyrrolidinone, which was confirmed by IR and ¹H-NMR spectroscopic data.

These results demonstrate a rapid versatile and selective reducing system for wide variety of nitro-compounds in the presence of other functional groups for e.g. -C ≡ N, > C = O, etc. Ammonium formate also has the advantages of being readily available, inexpensive, stable and nontoxic and can be used in conjunction with either Pd-C or Raney-Nickel catalysts. Moreover, it may be added to the reaction in a single portion and products can be easily separated from the reaction mixture. This procedure will therefore be of general use for the preparation of amines specifically in cases where rapid mild reduction is required.

ACKNOWLEDGMENTS

Research was supported by NCI Training Grant #5-T32-CA09015-08 and by NINCDS grant #P01 NS15655-04.

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(a) Raney-Nickel-H₂O in Parr apparatus (b) Fe powder - aqueous acetic acid (c) SnCl₂·2H₂O - conc. HCl:CH₃OH.

(Received in USA 11 April 1984)