A Facile Synthesis of α-Amino Esters via Reduction of α-Nitro Esters Using Ammonium Formate as a Catalytic Hydrogen Transfer Agent[1]

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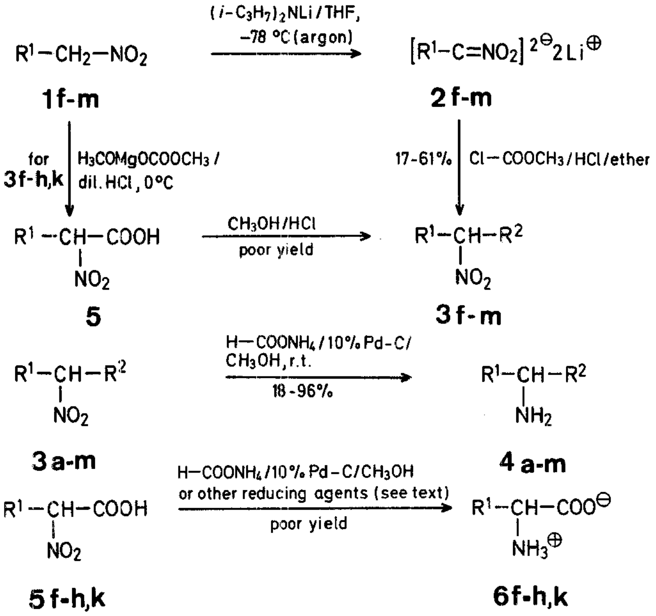
Various nitroesters **3** were selectively and rapidly reduced to their corresponding amino esters **4** in very good yield using anhydrous ammonium formate as a catalytic hydrogen transfer agent.

Radiolabelled α-amino acids have been used to investigate amino acid metabolism in the brain and other organs, e.g. DL-[^{11}C-carboxyl]-tryptophan[2], DL-[^{11}C-carboxyl]-valine[2] and L-[^{11}C-methyl]-methionine[3] as pancreatic imaging, and 1-aminocyclopentane-1-[^{11}C]-carboxylic acid and 1-aminocyclobutane-1-[^{11}C]-carboxylic acid as tumor imaging[4] have been developed. Besides these, several other α-amino acids such as 1-aminocyclopropane-1-carboxylic acid[5,6] and 2,6-diaminopimelic acid[7,8] have considerable biological importance.

As a continuation of our ongoing program, we were interested in the radioisotopic synthesis of ^{11}C-α-amino acids (^{11}C-half-life = 20.4 min) especially ^{11}C-leucine for the tomographic measurement of protein synthesis in the human brain. For this purpose, we required α-nitro esters as intermediates, which could be rapidly reduced to the corresponding α-amino esters. In general the traditional syntheses[9-14] of α-nitro esters (except carboxylation procedures) are not applicable for the preparation of ^{11}C-α-nitro esters, due to limitation of short half-life and easy availability of the desired ^{11}C-precursors[15-18]. Further, reduction of α-nitro esters to α-amino esters is carried out either by catalytic hydrogenation[10,12,15,16,19-22] at high pressure/atmospheric pressure or by chemical reduction[10,18,23]. Catalytic hydrogenations usually require longer times, while chemical reductions, which are less studied in amino acid literature, provide poor yield of the desired product.

Recently ammonium formate has been successfully employed as catalytic hydrogen transfer agent in peptide chemistry for deprotection[24,25] in place of cyclohexene. Reduction of azides[26] and the cyano group[27] to corresponding amines and methyl group respectively has also been reported. We reported earlier[1] a general procedure for reduction of aliphatic and substituted aromatic nitro compounds to the corresponding amino derivatives using ammonium formate as a catalytic hydrogen transfer agent. We now report an extension of this new method for the efficient and rapid chemical reduction of α-nitro esters **3** to the corresponding α-amino esters **4** with ammonium formate.



The α-nitro esters **3f–m** were prepared by a modified procedure[18] (for the availability of **3a–l**, see experimental). Nitroalkanes **1f–m** on treatment with 2 mol of lithium diisopropylamide in dry tetrahydrofuran at −78 °C under argon gave dilithio-derivatives **2f–m**, which on reaction with methyl carbonochloridate at −78 °C afforded α-nitro esters **3f–m**. However, β-phenylnitroethane (**1l**) under similar conditions gave a mixture of two products; methyl α-nitro-β-phenylpropionate (**3l$_1$**) and methyl α-phenyl-β-nitropropionate (**3l$_2$**). The predominant formation of **3l$_2$** by carboxylation of the carbanion β to the nitro group is in agreement with work reported in the literature[28]. Alternatively α-nitro esters **3f–h, k** were also prepared[16] by the reaction of an appropriate nitroalkane **1** with methoxymagnesium methyl carbonate in dimethylformamide, followed by acidification with dilute hydrochloric acid to afford α-nitro acids **5**. The α-nitro acids **5** on esterification with saturated methanolic hydrogen chloride gave corresponding α-nitro esters **3** in poor yield. Purification of these α-nitro esters was carried out by silica gel chromatography using dichloromethane as eluent.

Compounds **3a–m** on reduction with ammonium formate in the presence of 10% palladium on carbon in methanol at room temperature provided excellent yields of corresponding amino esters **4a–m** within 10 min. The progress of reaction was monitored by T.L.C. analysis. The nitro ester pairs **3l$_1$** and **3l$_2$** as well as the corresponding amino ester pairs **4l$_1$** and **4l$_2$** have very close R_F values, hence could not be separated by column chromatography. However, the G.L.C. analysis of the mixture showed that the amino esters **4l$_1$** and **4l$_2$** are present in a ratio of 1 : 10.

The reduction of α-nitro acids **5** with other reducing agents for e.g. tin(II) chloride/hydrochloric acid, zinc/acetic acid, hydrazine/Raney nickel (acetate buffer : ethanol) as well as ammonium formate provides poor yields of α-amino acids **6**. These poor yields of α-amino acids can be attributed to rapid decarboxylation of α-nitro acids, which have been shown to be unstable in the aqueous and basic media[29]. Reduction of ethyl nitroacetate (**3a**) with hydrazine/Raney nickel in a variety of conditions gave poor yield of ethyl glycinate (**4a**); however reduction of α-nitro esters **3** with ammonium formate/palladium-on-carbon in methanol at room temperature afforded excellent yield of α-amino esters **4**. The isolated yields are based on single experiments and were not optimized. Further, this reduction was successfully applied to β- and γ-nitro esters **3e**, and **3b** and **3c** yielding their corresponding amino esters.

The end products were characterized by T.L.C., and G.L.C. as well as by I.R. and ^{1}H-N.M.R. spectroscopy. The spectral data agreed with those reported in the literature. The purity of the compounds was > 98% as determined by G.L.C. analysis [5% OV-101, column size 50 cm × 1/8″, temperature programmed 35–250 °C (two min hold at 35 °C followed by heating at 15°/min up to 250 °C), flow rate 20 ml helium/min]. The amino esters **4** were visualized on T.L.C. by ninhydrin. Some amino esters were converted into their hydrochlorides for isolation. Compounds **3a, b, d** and **3c** were purchased from Aldrich Chemical Company and ICN, respectively. Compound **3e** was prepared[30] by esterification of 3-nitropropionic acid with methanolic hydrogen chloride.

Table 1. Yields of Nitro Esters **3f–m** prepared by the Modified Procedure[18] and Chromatographic Data of **3a–m**

Compound	R^1	R^2	Yield[a] [%]	Retention time [min]	R_F Value[b]
3a	H	$COOC_2H_5$	–	3.78	–
3b	H	$CH_2CH_2COOCH_3$	–	4.85	0.10
3c	CH_3	$CH_2CH_2COOCH_3$	–	7.42	0.14
3d	$COOC_2H_5$	$COOC_2H_5$	–	8.51	0.25
3e	H	CH_2COOCH_3	–	6.18	0.18
3f	CH_3	$COOCH_3$	17	5.74	0.35
3g	C_2H_5	$COOCH_3$	32	6.62	0.25
3h	n-C_3H_7	$COOCH_3$	56	7.04	0.33
3i	n-C_4H_9	$COOCH_3$	61	7.95	0.47
3j	n-C_5H_{11}	$COOCH_3$	57	8.86	0.53
3k	i-C_4H_9	$COOCH_3$	53	7.38	0.44
3l$_1$	$C_6H_5-CH_2$	$COOCH_3$	47[c]	10.79	0.30
3l$_2$	H	$CH(C_6H_5)COOCH_3$			
3m	C_6H_5	$COOCH_3$	43	10.31	0.44

[a] These represent isolated yields based on single experiments and were not optimized. All the nitro esters were prepared on a very small scale and characterized as oils.

[b] Analtech silica gel plates, mobile phase: dichloromethane/hexane (1/1).

[c] Combined yield of both the products **3l$_1$** + **3l$_2$**.

Table 2. Amino Esters **4a–m** prepared

Product No.	Yield[a] [%]	R_F Value[b]	m.p. [°C]	Lit. m.p. [°C][c]
4a	64	0.98[e]	137°[f]	144°
4b	81	0.24	138°[f,g]	96–99°[32]
4c	75	0.25	oil	–[d]
4d	69	0.42	156–158°[f]	164–165°[33]
4e	79	0.15	oil	94–95°[f]
4f	67	0.34	155–157°[f]	158°
4g	67	0.44[e]	136–137°[f]	139°
4h	76	0.42	oil	–[d]
4i	78	0.34	hygroscopic[f]	–[d]
4j	88	0.41	hygroscopic[f]	–[d]
4k	96	0.41	132°[f]	118° (α-form), 150–151° (β-form) for (*S*)-enantiomer, 149–150° for (*R*)-enantiomer
4l$_1$	47[h]	0.38	oil (mixture)	158–162°[f]
4l$_2$				192–195°[f31]
4m	18[i]	0.37	oil	32°

[a] Isolated yields based on single experiments, not optimized.

[b] Analtech silica gel plates, mobile phase: CH_2Cl_2/CH_3OH (95/5).

[c] Unless otherwise mentioned, the literature data are taken from *Dictionary of Organic Compounds*, 5th Edn., Chapman and Hall, New York, 1982.

[d] Known compounds but no physicochemical data reported in the literature.

[e] Mobile phase: $CHCl_3/CH_3OH$ (9/1).

[f] Refers to hydrochlorides.

[g] Compound decomposes, when heated > 138 °C.

[h] Combined yield from reduction of a mixture of nitro esters, **3l$_1$** + **3l$_2$**.

[i] Poor yield of methyl phenylglycinate is due to the impurities present in the starting nitro ester.

α-Nitro-Esters 3f–m; General Procedure:

The appropriate nitroalkane **1** (0.02 mol) is added to a stirred suspension of lithium diisopropylamide (4.28 g, 0.04 mol) [prepared from 1.55 molar hexane solution of *n*-butyllithium (25.8 ml, 0.04 mol) and diisopropylamine (4.04 g, 0.04 mol) in dry tetrahydrofuran (15 ml) at – 78 °C under argon] and the stirring is continued for 30 min at – 78 °C under argon. To the resulting mixture, methyl carbonochloridate (1.99 g, 0.021 mol) is added, the stirring is continued for additional 90 min, and saturated ethereal hydrogen chloride (50–60 ml) is then added at – 78 °C. The inorganic material is filtered off and the residue is washed with ether (100 ml). The combined organic layer is evaporated at 60–70 °C and the resulting residue is purified twice by column chromatography on silica gel [silica gel, (50 g), 230–400 mesh, size of column 2.54 × 45 cm] eluting with dichloromethane. Appropriate fractions are combined and evaporated to give nitro esters **3f–m**.

Amino Esters 4; General Procedure:

To a stirred solution of the appropriate nitro ester **3** (5.7 mmol) in dry methanol (10 ml), is added 10% Pd-C (0.35 g–0.4 g), followed by anhydrous ammonium formate (1.96 g, 31 mmol) one portion. The resulting heterogeneous reaction mixture is stirred at room temperature for 10 min under argon. Ether (200 ml) is added and the catalyst is removed by filtration. The filtrate is washed with water (2 × 20 ml), the organic layer is dried with sodium sulfate and filtered. The filtrate is either evaporated at 35 °C under reduced pressure to give amino esters **4** or converted into their hydrochlorides.

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