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RAPID DEBENZYLATION OF N-BENZYLAMINO DERIVATIVES TO AMINO-DERIVATIVES USING AMMONIUM FORMATE AS CATALYTIC HYDROGEN TRANSFER AGENT[1,2]

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Summary: Various N-benzyl derivatives of amino acids and amines were deprotected to the corresponding free amino acids and amines using ammonium formate as the hydrogen source.

Catalytic transfer hydrogenation has been successfully applied for removal of a benzyl group from protected benzyloxycarbonyl, benzylester and benzylester derivatives of peptides and amino acids using cyclohexene,[3,4] 1,4-cyclohexadiene[5], hydrazine-hydrate[6] and ammonium formate[7,8] as the hydrogen donor. Deprotection of the N-benzyl group, however, is still most often carried out by traditional high pressure catalytic hydrogenation.[9,10] Recently, B. El Amin, et al.[11] reported that removal of a benzyl group from Z-amino acids using formic acid as the hydrogen donor, provides formate salts of amino acids as end products instead of free amino acids.

In our on-going program to develop rapid synthesis of radio-labeled tracer molecules for Positron Emission Tomography (PET), we are interested in the radioisotopic synthesis of ^{11}C-amino acids (^{11}C-half life=20.4 min) such as [^{11}C-carboxyl]-γ-amino butyric acid, [^{11}C-carboxyl]-β-alanine, etc. via N-benzyl derivatives of bromoalkanes. In this paper we wish to report a rapid deprotection of the N-benzyl group to the corresponding free amino derivatives using ammonium formate as shown in Scheme 1 (R=H/Alkyl; R_1=H/C_2H_5; n=1-3).

Scheme 1

$$C_6H_5CH_2NH(CHR)_nCO_2R_1 \xrightarrow[10\%\ Pd\text{-}C,\ CH_3OH]{HCO_2NH_4} H_2N(CHR)_nCO_2R_1$$

A typical procedure for debenzylation is as follows. To a stirred suspension of an appropriate N-benzyl compound (3 mmol) and an equal weight of 10% Pd-C in dry methanol (20 ml), anhydrous ammonium formate (15 mmol) was added in a single portion under nitrogen.

The resulting reaction mixture was stirred at reflux temperature and the reaction was monitored by TLC. After completion of reaction, the catalyst was removed by filtration through a celite pad, which was then washed with 20 ml of chloroform. The combined organic filtrate, on evaporation under reduced pressure, afforded the desired amino derivative. In the case of free amino acids, the reaction mixture was filtered while hot and the celite pad was washed with boiling water (20 ml). Characterization of this new procedure is shown in Table 1.

In most cases, the reaction is over within 6-10 min; however, for N-benzyl-2-methylimidazole, the reaction requires 60 min for completion. These results demonstrate a rapid and versatile system for removal of an N-benzyl group from a wide variety of compounds including protected amino acids under moderate reaction conditions.

Table 1. Debenzylation of N-benzyl Amino Derivatives to Corresponding Amine Derivatives

N-Benzyl Compounds (Bz=$CH_2C_6H_5$)	Products[b]	Reaction Time in Min	Yield[a] %	Relative R_f Values of Products[c]
$(CH_3)_2CHCH_2CH(CO_2H)NHBz$	$(CH_3)_2CHCH_2CH(CO_2^{\ominus})NH_3^{\oplus}$	6	96	0.47[f]
$CH_3CH_2CH(CH_3)CH(CO_2H)NHBz$	$CH_3CH_2CH(CH_3)CH(CO_2^{\ominus})NH_3^{\oplus}$	8	95	0.49[f]
$BzN(CH_2CO_2H)_2$	$NH(CH_2CO_2H)_2$	10	64	0.24[f]
$BzNHCH_2CO_2C_2H_5$	$NH_2CH_2CO_2C_2H_5$	<10	97	0.50[e]
$BzNH(CH_2)_3CO_2C_2H_5$	$NH_2(CH_2)_3CO_2C_2H_5$	6	95	0.39[e]
Ethyl N-benzylnipecoate	Ethyl nipecoate	10	91	0.31[e]
N-Benzyl-2-methylimidazole	2-Methylimidazole	60	97	0.18[d]

(a) Unoptimized, isolated yields are based on a single experiment; (b) charactertized via comparison with authentic samples (IR, ^{1}H-NMR, TLC and m.p.); (c) relative R_f value = distance travelled by product chromatograph/distance travelled by starting material chromatograph, using E Merck silica gel plates; mobile phase: $CHCl_3$:MeOH:58% NH_4OH; (d) 9:1:3 drops; (e) $CHCl_3$;MeOH (96:4); (f) BuOH:AcOH:H_2O (4:1:1).

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