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SHORT COMMUNICATIONS

Synthesis of *N*-*tert*-Butyl Amides by Reaction of *tert*-Butyl Bromide with Amides in the Presence of Manganese Compounds

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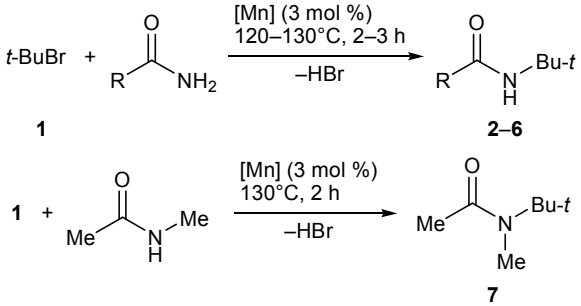
N-*tert*-Butyl amides are important compounds for pharmaceutical industry and are precursors of important drugs, such as Finasteride, Nelfinavir, Saquinavir, and some diarylbutanol derivatives, that are used for the treatment of prostatic hyperplasia and inhibit HIV protease [1].

A known method for the synthesis of *N*-*tert*-butyl amides is based on the Ritter reaction of nitriles with *tert*-butyl cation generated *in situ* from isobutylene or *tert*-butyl alcohol in the presence of a strong acid. However, these procedures are not free from some limitations; for instance, isobutylene is a gaseous substance under normal conditions, and it polymerizes on heating, while *tert*-butyl alcohol is a solid at room temperature. The most convenient reagent is *tert*-butyl acetate which reacts with nitriles at 20°C in the presence of stoichiometric amounts of sulfuric and acetic acids [2–4]. Analogous reaction was also accomplished in the presence of $FeCl_3 \cdot 6H_2O$ (10 mol %) at 150°C [5] and I_2 (20 mol %) (110°C, 4–6 h) [6] or trifluoroacetic acid (3–4 equiv) [7]. The reaction catalyzed by a stoichiometric amount of the boron trifluoride complex with poly(vinylpyrrolidone) PVP–BF_3 occurred under milder conditions (70°C) [8]. Syntheses of *N*-*tert*-butyl amides by reactions of alcohols or ethers with nitriles in the presence of heterogeneous catalysts, in particular $ZnCl_2/SiO_2$ (15 mol %) [9], P_2O_5/SiO_2 (60 wt %) [10], heteropolyacids, Amberlyst-15, Montmorillonite KSF, Zeolite HZSM-5 [11, 12], and ionic liquids [13], have also been reported.

Amides are known to react with tertiary hydrocarbyl halides. For example, the reaction of 1-bromoadamantane with formamide or acetamide at elevated temperature (185–195°C) [14] or in the presence of an equimolar amount of silver sulfate afforded 45% of the corresponding *N*-(adamantan-1-yl)-substituted amide [15].

We have recently shown that *N*-(adamantan-1-yl) amides are formed in 70–90% yield in the reactions of 1-bromoadamantane with carboxylic acid amides in the presence of manganese-containing catalysts at 120–130°C [16]. Taking into account practical importance of *N*-*tert*-butyl amides, we set ourselves the task of developing a procedure for their preparation via reaction of *tert*-butyl bromide with amides in the presence of metal complexes. As the latter we used the following manganese compounds: $MnCl_2$, $MnBr_2$, $Mn(OAc)_2$, $Mn(acac)_3$, and $Mn_2(CO)_{10}$. The conversion of *tert*-butyl bromide (**1**) and the yield of *N*-*tert*-butyl amides **2**–**7** depended on the catalyst. Among the examined manganese compounds, the best catalyst was $Mn_2(CO)_{10}$. The reactions with formamide were carried out at 120–130°C (2–3 h), the molar ratio *t*-BuBr–amide–catalyst being 100:(200 to 300):(1 to 3). Under the optimal conditions, the conversion of *tert*-butyl bromide (**1**) was 75%, and the only product was *N*-*tert*-butylformamide (**2**). Other carboxylic acid



2, R = H; **3**, R = Me; **4**, R = Et; **5**, R = Ph; **6**, R = $H_2NC(O)CH_2$.

Reaction of *tert*-butyl bromide (**1**) with carboxylic acid amides in the presence of manganese compounds

Catalyst	Amide	Molar ratio **1**–amide–Mn	Temperature, °C	Reaction time, h	Product no. (yield, %)
$MnCl_2$	$MeCONH_2$	100:300:3	130	3	**3** (54)
$MnBr_2$	$MeCONH_2$	100:300:3	130	3	**3** (67)
$Mn(OAc)_2$	$MeCONH_2$	100:300:3	130	2	**3** (90)
$Mn(acac)_3$	$MeCONH_2$	100:300:3	130	2	**3** (91)
$Mn(acac)_3$	$MeCONH_2$	100:200:3	130	2	**3** (82)
$Mn(acac)_3$	$MeCONH_2$	100:300:2	130	2	**3** (79)
$Mn(acac)_3$	$MeCONH_2$	100:300:3	120	3	**3** (92)
$Mn_2(CO)_{10}$	$MeCONH_2$	100:300:3	130	2	**3** (93)
$Mn_2(CO)_{10}$	$MeCONH_2$	100:300:3	120	3	**3** (89)
$Mn_2(CO)_{10}$	$MeCONH_2$	100:200:3	120	3	**3** (75)
$Mn_2(CO)_{10}$	$MeCONH_2$	100:300:1	120	4	**3** (68)
$Mn_2(CO)_{10}$	$MeCONH_2$	100:300:2	120	4	**3** (79)
$Mn_2(CO)_{10}$	$HCONH_2$	100:300:3	130	2	**2** (75)
$Mn_2(CO)_{10}$	$EtCONH_2$	100:300:3	130	2	**4** (92)
$Mn_2(CO)_{10}$	$PhCONH_2$	100:300:3	130	2	**5** (95)
$Mn_2(CO)_{10}$	$CH_2(CONH_2)_2$	100:300:3	130	2	**6** (64)
$Mn_2(CO)_{10}$	MeCONHMe	100:300:3	130	2	**7** (60)

amides, such as acetamide, propanamide, and benzamide, also readily reacted with *tert*-butyl bromide (**1**) under the above conditions, yielding 64–95% of the corresponding *N*-substituted amides **3**–**5** (see table). The amide nature appreciably affected the reaction selectivity and yield of the target product. Benzamide possessing a bulky benzene ring reacted with **1** to give *N*-*tert*-butylbenzamide (**5**) in 95% yield. The reaction of malonamide with *t*-BuBr was highly selective, and *N*-*tert*-butylmalonamide (**6**) was obtained in 64% yield. In all cases, liberated hydrogen bromide did not form salts with amides but evolved as gaseous product. The reaction of **1** with *N*-methylacetamide gave 60% of *N*-*tert*-butyl-*N*-methylacetamide (**7**).

The progress of the reaction was monitored by GLC. Optimal reactant concentrations and reaction conditions were found. Initial amides were taken in 2–3-fold excess, for they simultaneously acted as solvent (the reactions with solid amides were carried out in melt). The structure of amides **2**–**7** was confirmed by spectral data (IR, ^{13}C NMR, GC/MS) and comparison with authentic samples and published data. *N*-*tert*-Butyl amides **2**–**7** were purified from impurities by silica gel column chromatography using hexane–ethyl acetate as eluent; the yields are given for the isolated product.

***N*-*tert*-Butyl amides 2–7 (*general procedure*).** A 17-mL stainless steel high-pressure micro reactor or a glass ampule (the results of parallel runs differed insignificantly) was charged under argon with 0.3 mmol of manganese catalyst, 10 mmol of *tert*-butyl bromide (**1**), and 30 mmol of the corresponding amide. The reactor was hermetically closed (the ampule was sealed) and heated for 3–4 h at 120–130°C under continuous stirring. When the reaction was complete, the reactor (ampule) was cooled to room temperature and opened, the mixture was washed with water and extracted with methylene chloride (3×5 mL), the extract was evaporated under reduced pressure, and the residue was recrystallized.

***N*-*tert*-Butylformamide (2).** Yield 75%, bp 81–82°C (10 mm); published data [17]: bp 82–85°C (14 mm). IR spectrum (film), ν, cm^{-1}: 3278 (NH), 1643 (C=O), 1559 (NH). ^{13}C NMR spectrum, δ_C, ppm: 30.79 (CH_3), 50.90 (CNH), 163.33 (C=O).

***N*-*tert*-Butylacetamide (3).** Yield 93%, mp 97–98°C (from EtOH) [17]. IR spectrum (mineral oil), ν, cm^{-1}: 3284 (NH), 1640 (C=O), 1555, 1223, 606 (NH). ^{13}C NMR spectrum, δ_C, ppm: 25.22 ($CO\mathbf{C}H_3$), 29.04 (CH_3), 50.97 (CNH), 171.75 (C=O).

***N*-*tert*-Butylpropanamide (4).** Yield 92%, mp 83–84°C (from EtOH) [18]. IR spectrum (mineral oil), ν,

cm^{-1}: 3300 (NH), 1650 (C=O), 1550 (NH). ^{13}C NMR spectrum, δ_C, ppm: 8.26 (**C**H_3CH_2), 28.92 (CH_3), 31.42 (CH_2), 51.28 (CNH), 172.53 (C=O).

***N-tert*-Butylbenzamide (5).** Yield 95%, mp 135–136°C (from EtOH) [8]. IR spectrum (mineral oil), ν, cm^{-1}: 3438 (NH), 1655, 1663 (C=O), 1580 (C=C_{arom}), 1515 (δNH). ^{13}C NMR spectrum, δ_C, ppm: 29.32 (CH_3), 51.53 (CNH); 126.83, 128.59, 131.36, 135.92 (C_{arom}); 168.06 (C=O).

***N-tert*-Butylpropanediamide (6).** Yield 64%, mp 145–146°C. IR spectrum (mineral oil), ν, cm^{-1}: 3284 (NH), 1650 (C=O), 1555 (NH). ^{13}C NMR spectrum, δ_C, ppm: 29.84 (CH_3), 45.05 (CH_2), 50.12 (CNH), 165.23 (C=O), 175.36 (C=O). Found, %: C 52.82; H 8.78; N 17.44. $C_7H_{14}N_2O_2$. Calculated, %: C 53.15; H 8.92; N 17.71.

***N-tert*-Butyl-*N*-methylacetamide (7).** Yield 60%, bp 70–71°C (14 mm); published data [19]: bp 56.5°C (5 mm). IR spectrum (film), ν, cm^{-1}: 3290 (NH), 1645 (C=O), 1555 (NH). ^{13}C NMR spectrum, δ_C, ppm: 26.48 (CH_3), 28.85 (CH_3), 30.96 [C(**C**$H_3)_3$], 54.96 (CNH), 174.50 (C=O).

The IR spectra were recorded on a Bruker Vertex 70V spectrometer. The ^{13}C NMR spectra were measured on a Bruker Avance-400 spectrometer at 100.62 MHz using $CDCl_3$ as solvent. The mass spectra were obtained on a Shimadzu GCMS-QP2010 Ultra instrument (Supelco PTE-5 capillary column, 60 m× 0.25 mm; carrier gas helium; oven temperature programming from 40 to 280°C at a rate of 8 deg/min; injector temperature 260°C; ion source temperature 200°C; electron impact, 70 eV). The elemental compositions were determined on a Carlo Erba 1106 analyzer. The progress of reactions was monitored, and the purity of products was checked, by GLC on Shimadzu GC-9A and GC-2014 instruments (2-m× 3-mm column packed with 5% of SE-30 on Chromaton N-AW-HMDS; oven temperature programming from 50 to 270°C at a rate of 8 deg/min; carrier gas helium, flow rate 47 mL/min).

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