Research Article

An Efficient Method for Synthesis of *N*-*tert*-Butyl Amides Using Oxalic Acid Dihydrate in Solvent-Free Condition

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An efficient method for the synthesis of *N*-*tert*-butyl amides by reaction of nitriles with *tert*-butyl acetate or *tert*-butanol is described using oxalic acid dihydrate in solvent-free condition. The result showed that *tert*-butyl acetate served as a relatively better source of *tert*-butyl carbocation than *tert*-butanol.

1. Introduction

Solvent-free reactions obviously reduce pollution and bring down handling costs due to simplification of experimental procedure, work-up technique, and saving energy. These would be especially important during industrial production [1]. The Ritter reaction makes possible the conversion of a group, capable of giving a relatively stable carbonium ion, to a substituted amide by reaction with a nitrile in the presence of a strong acid [2]. The classical Ritter reaction is the reaction of alkenes and tertiary or benzylic alcohols with nitriles in the presence of concentrated sulfuric acid [3–5]. Several modifications have been attempted to improve Ritter reaction conditions. However, as an alternative to sulfuric acid, other acid catalysts such as (CF₃SO₂)₂O [6], BF₃·Et₂O [7], Fe³⁺-Montmorillonite [8], Mg(HSO₄)₂ [9], Bi(OTf)₃ [10], CeCl₃·7H₂O/AcCl [11], P₂O₅/SiO₂ [12], and Nafion [13] are employed in the classical Ritter reaction. Ritter reaction using *tert*-butyl acetate instead of alcohol was also reported to be catalyzed by sulfuric acid [14, 15], FeCl₃·6H₂O [16], ZnCl₂-SiO₂ [17], and I₂ [18]. However, most of these methods suffer from at least one of the following disadvantages such as vigorous reaction conditions, high cost

and toxicity of the reagent, tedious work-up procedures, and instability and hygroscopic nature of the reagent. Also, the use of *tert*-butanol can be complicated by the melting point (26°C) leading to a semisolid at room temperature. An attractive alternative is *tert*-butyl acetate due to its ease of handling (bp 97–98°C), availability as a common solvent, and low cost [15]. Recently, oxalic acid was efficiently used as catalyst in variety of chemical reactions like imino Diels-Alder reaction [19], Beckmann rearrangement [20], protection of carbonyl to thioacetal, and deprotection of thioacetal to carbonyl as well [21]. The conversion of a nitrile to the corresponding *N*-*tert*-butyl amide is a very important transformation in organic synthesis. The *N*-*tert*-butyl amides are pharmaceutically useful [22] and also serve as precursors to the corresponding amines. In connection of our research to develop application of oxalic acid dihydrate for oxygenation of sulfides to sulfoxides in the presence of H₂O₂ [23], herein, we found that oxalic acid dihydrate can be used for preparation of *N*-*tert*-butyl amide derivatives in good yields. This method often leads to the development of simple and ecofriendly protocols for preparation of *N*-*tert*-butyl amides via modified Ritter reaction. Amidation of

TABLE 1: Amidation of *tert*-butylacetate or *tert*-butanol with nitriles using oxalic acid dehydrate.

Entry	Substrate	Nitrile	Amide ^a	Time/h	Yield % ^b
a	(CH ₃) ₃ COAc	C ₆ H ₅ CN	C ₆ H ₅ CONH ^t Bu	2	90
a'	(CH ₃) ₃ COH	C ₆ H ₅ CN	C ₆ H ₅ CONH ^t Bu	2.30	88
b	(CH ₃) ₃ COAc	<i>p</i> -Cl-C ₆ H ₄ CN	<i>p</i> -Cl-C ₆ H ₄ CONH ^t Bu	2	92
b'	(CH ₃) ₃ COH	<i>p</i> -Cl-C ₆ H ₄ CN	<i>p</i> -Cl-C ₆ H ₄ CONH ^t Bu	3	90
c	(CH ₃) ₃ COAc	<i>p</i> -Me-C ₆ H ₄ CN	<i>p</i> -Me-C ₆ H ₄ CONH ^t Bu	2	88
c'	(CH ₃) ₃ COH	<i>p</i> -Me-C ₆ H ₄ CN	<i>p</i> -Me-C ₆ H ₄ CONH ^t Bu	2.30	85
d	(CH ₃) ₃ COAc	<i>m</i> -Me-C ₆ H ₄ CN	<i>m</i> -Me-C ₆ H ₄ CONH ^t Bu	2	94
d'	(CH ₃) ₃ COH	<i>m</i> -Me-C ₆ H ₄ CN	<i>m</i> -Me-C ₆ H ₄ CONH ^t Bu	2	92
e	(CH ₃) ₃ COAc	<i>p</i> -HO-C ₆ H ₄ CN	<i>p</i> -HO-C ₆ H ₄ CONH ^t Bu	4	76
e'	(CH ₃) ₃ COH	<i>p</i> -HO-C ₆ H ₄ CN	<i>p</i> -HO-C ₆ H ₄ CONH ^t Bu	4	70
f	(CH ₃) ₃ COAc	<i>p</i> -NC-C ₆ H ₄ -CN	<i>p</i> - ^t BuNHOC-C ₆ H ₄ CONH ^t Bu	4.30	92 ^c
f'	(CH ₃) ₃ COH	<i>p</i> -NC-C ₆ H ₄ -CN	<i>p</i> - ^t BuNHOC-C ₆ H ₄ CONH ^t Bu	5	90 ^c
g	(CH ₃) ₃ COAc	<i>m</i> -NC-C ₆ H ₄ -CN	<i>m</i> - ^t BuNHOC-C ₆ H ₄ CONH ^t Bu	4.30	88 ^c
g'	(CH ₃) ₃ COH	<i>m</i> -NC-C ₆ H ₄ -CN	<i>m</i> - ^t BuNHOC-C ₆ H ₄ CONH ^t Bu	5	86 ^c
h	(CH ₃) ₃ COAc	CH ₂ =CHCN	CH ₂ =CHCONH ^t Bu	3	66
h'	(CH ₃) ₃ COH	CH ₂ =CHCN	CH ₂ =CHCONH ^t Bu	4	60
i	(CH ₃) ₃ COAc	ClCH ₂ CN	ClCH ₂ CONH ^t Bu	3.5	45
i'	(CH ₃) ₃ COH	ClCH ₂ CN	ClCH ₂ CONH ^t Bu	4	42
j	(CH ₃) ₃ COAc	NCCH ₂ COOEt	^t BuNHCOCH ₂ COOEt	3.5	54
j'	(CH ₃) ₃ COH	NCCH ₂ COOEt	^t BuNHCOCH ₂ COOEt	4	48
k	(CH ₃) ₃ COAc	CH ₃ CN	CH ₃ CONH ^t Bu	8	48
k'	(CH ₃) ₃ COH	CH ₃ CN	CH ₃ CONH ^t Bu	9	45

^a All entries were carried on nitrile (5 mmol), oxalic acid dehydrate (2.5 mmol) and *t*-BuOAc or *t*-BuOH (5 mmol) at 70 °C. ^b All yields refer to isolated products.

^c Nitrile (2.5 mmol) is used.

tert-butyl acetate or *tert*-butanol with nitriles using oxalic acid dihydrate,

where R = alkyl, aryl, R' = -COCH₃, H.

2. Materials and Measurements

All chemicals were purchased from Merck chemical company. Melting points were recorded on an electrothermal melting point apparatus. The NMR spectra were recorded in CDCl₃ with TMS as an internal standard on a Bruker advance DRX 400 MHz spectrometer. IR spectra were determined on a SP-1100, P-UV-Com instrument. Elemental analyses were performed using a CHN-O Rapid Heraeus elemental analyser (Wellesley, MA). Purity determination of the products was accomplished by TLC on silica gel polygram SIL G/UV 254 plates. Products were identified by comparison of the obtained FT-IR and ¹H NMR spectra with those reported for authentic samples.

3. Experimental

3.1. General Procedure for the Amidation Reaction. A solution of 5 mmol nitrile in 5 mmol *tert*-butyl acetate or *tert*-butanol was prepared. 2.5 mmol oxalic acid dihydrate was added to the solution and the reaction mixture was stirred for 2–9 h under 70 °C until TLC analysis showed that no nitrile remained. The solid residue was recrystallized from water to afford pure crystals of the proper amides in 42–94% yields.

3.2. Characterization Data

3.2.1. *N*-*tert*-Butyl-3-methylbenzamide (d). M.p.: 96–97 °C. IR (KBr) ν : 3382, 2962, 1643, 1529, 1447, 748 cm⁻¹. ¹H NMR (400 MHz CDCl₃) δ = 1.49 (s, 9H), 2.4 (s, 3H), 5.95 (br s, 1H), 7.28–7.56 (m, 4H) ppm. Anal. Calcd. For C₁₂H₁₇NO: C, 75.35; H, 8.91; N, 7.32. Found: C, 75.15; H, 8.71; N, 7.22.

3.2.2. *N*-*tert*-Butyl-4-hydroxybenzamide (e). M.p.: 189–192 °C. FT-IR (KBr): ν = 3274, 3068, 2969, 1639, 1548, 1307, 935 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.49 (s, 9H), 5.97 (br s, 1H), 6.84 (d, 2H), 7.59 (d, 2H) ppm. Anal. Calcd. For C₁₁H₁₅NO₂: C, 68.36; H, 7.82; N, 7.25. Found: C, 67.85; H, 7.37; N, 6.92.

3.2.3. *N*¹,*N*⁴-di-*tert*-Butylterephthalamide (f). M.p.: 272–276 °C. FT-IR (KBr): ν = 3301, 2969, 1639, 1546, 1324, 864 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.50 (s, 18H), 5.97

(br s, 2H), 7.77 (s, 4H) ppm. Anal. Calcd. For $C_{16}H_{24}N_2O_2$: C, 69.52; H, 10.13; N, 8.75. Found: C, 68.95; H, 9.47; N, 7.98.

3.2.4. N^1, N^3 -di-*tert*-Butylisophthalamide (g). M.p.: 204–207°C. IR (KBr) ν : 3272, 3068, 2969, 1639, 1548, 1307, 680 cm^{-1} . 1H NMR (400 MHz $CDCl_3$) δ = 1.49 (s, 18H), 6 (br s, 2H), 7.28–8.11 (m, 4H) ppm. Anal. Calcd. For $C_{16}H_{24}N_2O_2$: C, 69.52; H, 10.13; N, 8.75. Found: C, 68.87; H, 9.67; N, 8.18.

4. Results and Discussion

A variety of *N-tert*-butyl amides were prepared from *tert*-butyl acetate with nitriles in the presence of oxalic acid dihydrate in good yields. In order to show the merit of the catalyst for Ritter reactions, we have also studied the reaction of several aromatic nitriles with *t*-BuOH. The results were satisfactory and the aromatic nitriles proceeded well in good yields (Table 1, entries a–g'). Acrylonitrile and aliphatic nitriles were converted to the corresponding amides in moderate yields in both reaction conditions (Table 1, entries h–k'). It is worth mentioning that the corresponding amide in each case was isolated by simple crystallization from the crude product.

The formation of *tert*-butyl amides in good yields and shorter time as seen from Table 1 shows that *tert*-butyl acetate served as a relatively better source of *tert*-butyl carbocation. Greatly facilitated heterolytic cleavage of C–O bond of *tert*-butyl acetate by oxalic acid dihydrate is rationalized by the leaving group superiority of acetate over OH group.

5. Conclusions

In conclusion, we have developed a simple, inexpensive, and ecofriendly methodology for modified Ritter reaction that represents effective activity for the amidation of *tert*-butyl acetate and *tert*-butanol with nitriles. This method provides an easy access to a variety of *tert*-butyl amides.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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