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A facile method for the preparation of oxime *t*-butyl carbonates for evaluation of the Beckman rearrangement

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ABSTRACT

Several oxime t-butyl carbonates were prepared conveniently in good yields (71%-92%) by treatment of the proper alkyl and aryl oximes with $(Boc)_2O$ in the presence of NaH at room temperature. The oxime carbonates were used for evaluation of the Beckman rearrangement.

Key words: Oxime, *t*-butyl carbonate, Beckman rearrangement.

INTRODUCTION

Under the influence of variety of acidic reagents, oximes (1, Fig. 1) rearrange to substituted amides and lactams, a reaction termed as Beckman rearrangement. The reaction is stereo-specific and the group that normally migrates is one that is *anti* with respect to the hydroxyl group[1].

The use of acidic reagents for the Beckman rearrangement, prevents its application to sensitive substrates, therefore milder condition is required for the sensitive substrates[2,3].

Oximes and protected oximes in aqueous and nonaqueous medium rearrange and produce different products[4].

One of the substrates used in milder condition in the Beckman rearrangement is oxime ethyl carbonate (OEC) which can be prepared using either toxic and expensive reagents such as: $COCl_2$, $ClCO_2CCl_3$, $Cl_3COCOCCl_3$ or ethyl chloroformates.[5] Oxime ethyl carbonates under treatment with boron trifluoride etherate undergo the Beckman rearrangement to amides and lactames.[5] It was also reported that in presence of boron trifluoride etherate, benzophenone oxime undergoes rearrangement (Scheme 1)[6].

The mechanism of this rearrangement is still under question and more studies are required to clarify the mechanistic aspect of this reaction. The possible mechanism proposed by Anilkumar et al.[6] for this type of substrates is the nucleofuge and the migrating group are *anti* and the nucleofuge should be able to assist the migration process via coordination to the developing cationic center which is shown in transition state 2 (Fig. 1).

As proposed in the Beckman rearrangement of oxime ethyl carbonate 3, the oxygen atom of the alkoxy group coordinates and assists the migration. In order to evaluated the credibility of this mechanism, we synthesized rather bulky oxime carbonates namely oxime t-butyl carbonates (4) for the Beckman rearrangement studies under the same condition.

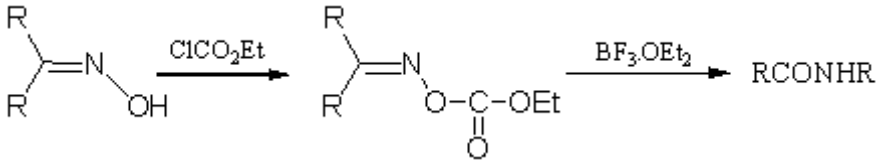
RESULTS AND DISCUSSION

Several aliphatic and aromatic oxime t-butyl carbonates were prepared by the reaction of *t*-butyl dicarbonate $(Boc)_2O$ and NaH at room temperature to provide the related carbonates in good yields (Table 1, Scheme 2). The structure of all oxime t-butyl carbonates were established by spectroscopic analysis (IR, 500MHz ^1H NMR).

Oxime *t*-butyl carbonates thus obtained were treated with 1 eq. of $BF_3.OEt_2$ in CH_2Cl_2 under Argon atmosphere. Prolonged subjection (8-12 h) of the oxime carbonates to the reaction condition reconverted them to the corresponding starting oximes and no trace of the expecting amide or lactams could be detected in the reaction products (Scheme 3).

Therefore this led us to conclude that in this type of substrates the bulkiness of alkoxy group plays a vital role in the Beckman rearrangement. Because of the steric effects of *t*-butyl group that prevent the coordination of alkoxy moiety and therefore participation in an intermediate such as 2, the rearrangement is inhibited.

On the other hand *t*-butoxycarbonyl group is one of the most important amino protecting group in peptide synthesis. Many *t*-butoxycarbonylating reagents[7] have been prepared as substitutes for *t*-butyl azidoformate,[8] which is toxic, shock-sensitive, and relatively unreactive.[9] 2-*t*-Butoxycarbonyloxyimino-2-phenylacetonitrile (6),[10] is one of such reagents. The usual method for the synthesis of this reagent uses toxic compounds such as phosgene and pyridine (Scheme 4).



Scheme 1

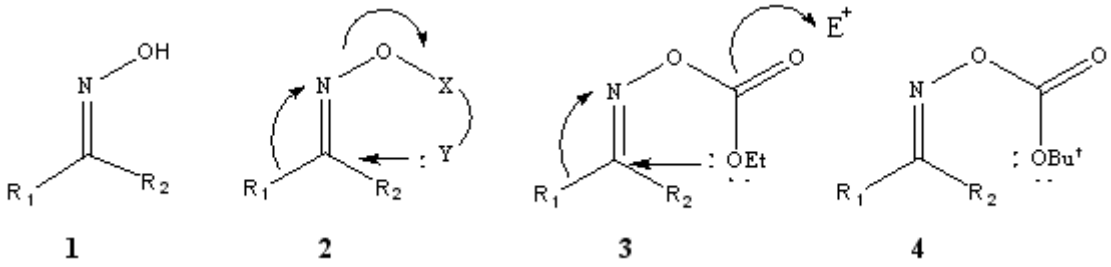
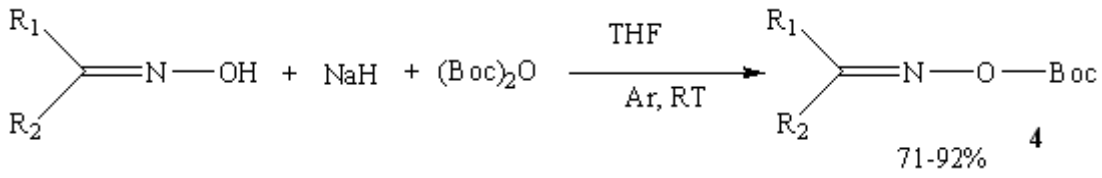


Fig. 1

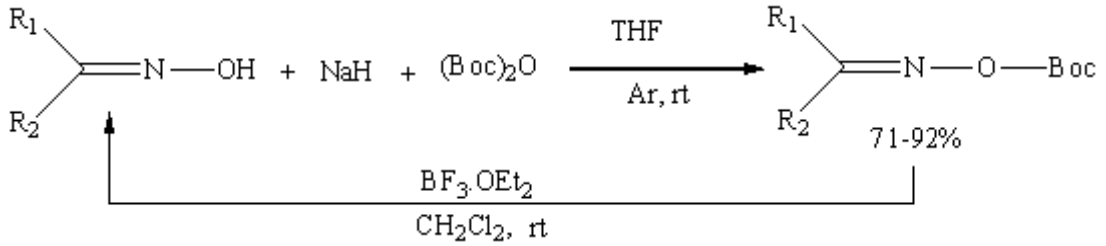


Scheme 2

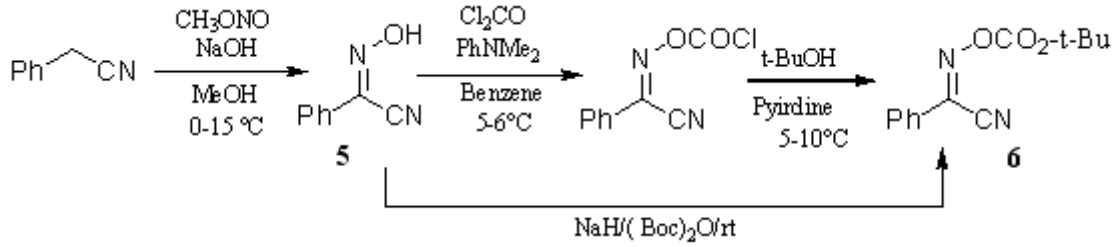
We developed an efficient method for the synthesis of 2-*t*-butoxycarbonyloxyimino-2-phenylacetonitrile (6) (Scheme 4). 2-Hydroxyimino-2-phenylacetonitrile (5) was prepared by a known procedure[11] and used for the preparation of 2-*t*-butoxycarbonyloxyimino-2-phenyl-acetonitrile (6) employing our method (reagent: NaH/$(Boc)_2O$). This method not only furnished the desired product in high yield 91% but also had the advantage of avoiding the use of toxic reagents and reducing reaction steps (Scheme 4).

As a part of our efforts to introduce this method for the preparation of O-substituted oximes using a suitable base, we also examined Bu^tOK. In a typical experiment, an equimolar mixture of acetophnone oxime and $(Boc)_2O$ were treated with Bu^tOK (0.5% mol) in Bu^tOH (15 mL). The reaction produced acetophenone oxime *t*-butyl carbonate in 78% yield by the following mechanism (Scheme 5).

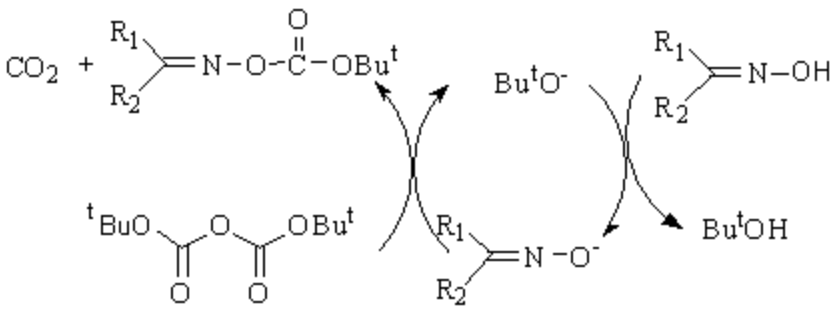
In summary we developed a convenient method for the preparation of several oxime *t*-butyl carbonates in good yields (71-92%) and used them



Scheme 3



Scheme 4



Scheme 5

as model compounds for the evaluation of the steric effects of alkoxy moiety in the Beckman rearrangement of oxime alkyl carbonates. Also we found that this procedure can be used as a suitable method for the protection and deprotection of oxime *t*-butyl carbonates.

Typical procedure for the preparation of oxime *t*-butyl carbonates

To a stirred solution of the oxime (5 mmol) in THF (15 mL), NaH (0.2-0.3 gr) was added under Ar atmosphere at room temperature. To this mixture $(Boc)_2O$ (5 mmol) was added and stirring continued for the required time (Table 1). The mixture was filtered and the filterate was evaporated to provide the related oxime carbonates which were purified by either recrystalization ($EtOH/H_2O$) or column chromatography (ethyl acetate/hexane).

4a. White solid, mp= 128-130°C; υ_{max}: 3100, 2920, 1765 (C=O), 1610 (C=N), 1250, 750, 690 cm^{-1}; δ_H: 1.56 (s, 9H), 7.39 (m, 4H), 7.50 (m, 4H), 7.61 (m, 2H) ppm.

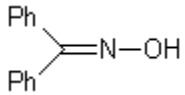
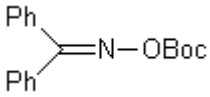
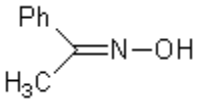
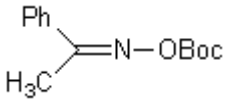
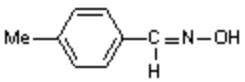
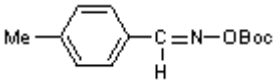
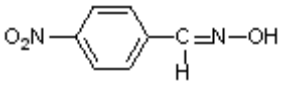
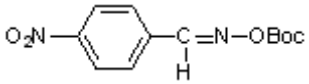
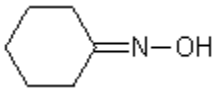
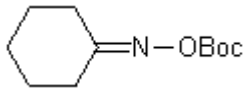
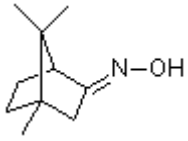
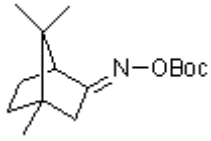
4b. Colorless oil, υ_{max}: 3080, 2930, 1780 (C=O), 1615 (C=N), 745, 690 cm^{-1}; δ_H: 1.61 (s, 9H), 2.42 (s, 3H), 7.45 (m, 3H), 7.78 (m, 2H) ppm.

4c. White solid, mp= 82-84°C; υ_{max}: 3050, 2980, 1758 (C=O), 1605 (C=N) cm^{-1}; δ_H: 1.57(s, 9H), 2.39 (s, 3H), 7.21 (d, *J*= 8.2 Hz, 2H), 7.61 (d, *J*= 8.2 Hz, 2H), 8.28 (s, 1H) ppm.

4d. Off white solid, mp= 132-134°C; υ_{max}: 1770 (C=O), 1605 (C=N), 1520, 1360 cm^{-1}; δ_H: 1.63 (s, 9H), 7.96 (d, *J*= 6.93 Hz, 2H), 8.33 (d, *J*= 6.93, 2H), 8.44 (s, 1 H) ppm.

4e. Colorless oil; υ_{max}: 2920, 1760 (C=O), 1605 (C=N), 1455, 1365, 1125 cm^{-1}; δ_H: 1.19(s, 9 H), 1.30 (m, 4 H), 1.29 (m, 6 H) ppm.

Table 1: Preparation of Oxime t-Butyl carbonates

Entry	Oxime	Time (h)	%Yield of 4a	Product
a		6	75	
b		5	71	
c		3.5	84	
d		3.5	92	
e		6	78	
f		6	73	

[a]Isolated yields

4f. Colorless oil; υ_{max}: 2980, 1780 (C=O), 1605 (C=N), 1460, 1350 cm^{-1}; δ_H: 1.11-1.82 (m, 25 H) ppm.

5: Light brown solid; mp= 118-120 °C (119-122)[11], δ_{max}: 3500 (OH), 2980, 2250 (Ca≡N), 1580 (C=N), 1497, 1450, 1420, 1280, 1062, 986, 765, 683 cm^{-1}; δ_H: 7.88 (d, *J*= 7.8 Hz, 2H), 7.56 (m, 3H), 4.80 (s, 1H)

6: White needles, mp= 82-84 (84-86)[11], υ_{max}: 3100, 2970, 2820, 2250 (Ca≡N), 1760, 1610, 1498, 1450, 1419, 1282, 1060, 968, 765, 688 cm^{-1}, δ_H: 7.91 (d, *J*= 8.2 Hz, 2H), 7.52 (m, 3H), 1.60 (s, 9H) ppm.

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