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A Useful Reagent for the Beckmann Rearrangement and the Synthesis of Nitriles from Carboxamides: *N,N'*-Carbonyldiimidazole and Reactive Halides

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Ketoximes undergo the Beckmann rearrangement and primary carboxamides are dehydrated to nitriles on treatment with *N,N'*-carbonyldiimidazole and an excess of reactive halide. The reaction can be carried out in high yields under neutral reaction conditions by a simple procedure; quaternization of the imidazole ring with reactive halides effectively promotes the reaction.

Keywords—Beckmann rearrangement; oxycarbonylimidazolium moiety; oxycarbonylimidazole moiety; *N,N'*-carbonyldiimidazole; ketoxime; primary carboxamide; quaternization; nitrile synthesis

We have recently reported a novel one-step conversion of alcohols into alkyl halides.¹⁾ In the reaction, 1-alkoxycarbonylimidazolium salts, which were obtained by the quaternization of nitrogen in the imidazole ring of 1-alkoxycarbonylimidazoles with reactive halides, were easily cleaved with decarboxylation to give the corresponding alkyl halides in high yields. Furthermore, we also found that the oxycarbonylimidazolium moiety (**1**) obtained by quaternization of the oxycarbonylimidazole moiety became an efficient leaving group, with decarboxylation (Chart 1).

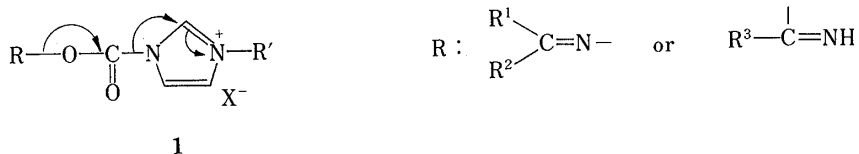


Chart 1

We report here some applications of this method to the Beckmann rearrangement and the synthesis of nitriles by the dehydration of primary carboxamides.

The Beckmann Rearrangement

The Beckmann rearrangement is usually carried out in the presence of certain acids, including Lewis acids.²⁾ There are only a few examples of the rearrangement under neutral conditions, *e.g.* using 2-fluoropyridinium salt or 2-chloropyrimidinium salt,³⁾ and *N,N'*-carbonyldiimidazole.⁴⁾ The former are quite efficient reagents, but are not commercially available, and the latter is not always satisfactory because the ability of the reagent to induce the rearrangement is weak.

We would like to report a useful improved method for the Beckmann rearrangement of ketoximes (**2**) using *N,N'*-carbonyldiimidazole (CDI) and reactive halides (*R'*-X) under mild conditions to give the carboxamides (**3**) (Chart 2).

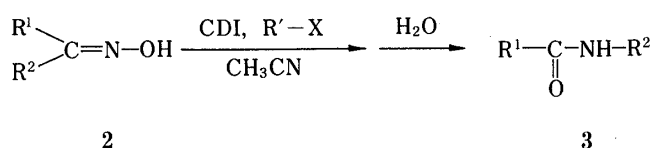


Chart 2

TABLE I. The Beckmann Rearrangement with *N,N'*-Carbonyldiimidazole and Reactive Halides

| Ketoxime 2 | | Reaction conditions | | Product 3 or 5 | Isolated yield (%) |
|-------------------|--|---------------------|---------------------|------------------|--------------------|
| R ₁ | R ₂ | | | | |
| Me | <i>p</i> -MeOC ₆ H ₄ | Reflux | 0.5 h ^{a)} | 3a | 92.5 |
| | | [Reflux | 2 h | 5a | 77 ^{b)} |
| Ph | Ph | Reflux | 1.5 h ^{a)} | 3b ^{e)} | 80 |
| PhCH ₂ | PhCH ₂ | Reflux | 1 h ^{c)} | 3c ^{e)} | 93 |
| | | Reflux | 1 h ^{a)} | 3d ^{e)} | 81.5 |
| Et | Ph | Reflux | 1 h ^{c)} | 3e ^{e)} | 93 |
| | | Reflux | 1 h ^{d)} | 3e ^{e)} | 98 |

a) 4 eq of allyl bromide was used.

b) The reaction was carried out in the absence of allyl bromide.⁷⁾

c) 5 eq of allyl bromide was used.

d) 5 eq of methyl iodide was used.

e) These carboxamides were identical in terms of IR and NMR spectra with authentic commercial samples.

Thus, the ketoximes (2) were treated with 1 eq of CDI and 4–5 eq of a reactive halide such as allyl bromide or methyl iodide in acetonitrile under heating for 0.5–1.5 h, and then water was added to afford the corresponding carboxamides (3) in high yields. The results are summarized in Table I. The reaction of the ketoximes (2) with CDI under the same conditions in the absence of R'-X gave only *O*-(1-imidazolylcarbonyl)oximes (5)⁴⁾ and the rearranged products were not obtained.

The advantage of this procedure is that the Beckmann rearrangement proceeds easily under neutral reaction conditions using commercially available reagents, and the procedure is simple. A plausible mechanism of this reaction is as follows. The nitrogen atom in the imidazole ring of the oxycarbonylimidazole (5), which is produced from the ketoxime (2) and CDI (path A) or the imidazolium salt (4) (path B), is quaternized with R'-X to afford the oxycarbonylimidazolium salt (6). The oxycarbonylimidazolium moiety of 6 is far more active as a leaving group than the oxycarbonylimidazole moiety, and the Beckmann rearrangement proceeds with decarboxylation under heating to produce the imino halide (7). The halide (7) gives the corresponding carboxamide (3) on treatment with water (Chart 3).

The Synthesis of Nitriles by the Dehydration of Primary Carboxamides

The dehydration of primary carboxamides is one of the best methods for the synthesis of nitriles, and many dehydrating agents are used for this purpose.⁵⁾ Ogata *et al.*⁶⁾ reported that the carboxamide group could react with *N,N'*-thionyl diimidazole, but could not react with *N,N'*-carbonyldiimidazole (CDI).

We found a new method for the synthesis of nitriles from primary carboxamides with CDI in the presence of an excess of R'-X (Chart 4). In this reaction, carboxamides (8) were treated with an excess of CDI (2 eq) and R'-X (8 eq) in acetonitrile under heating to afford the corresponding nitriles (9) in high yields. The results are shown in Table II. The reaction proceeds under neutral reaction conditions using commercially available reagents, and the

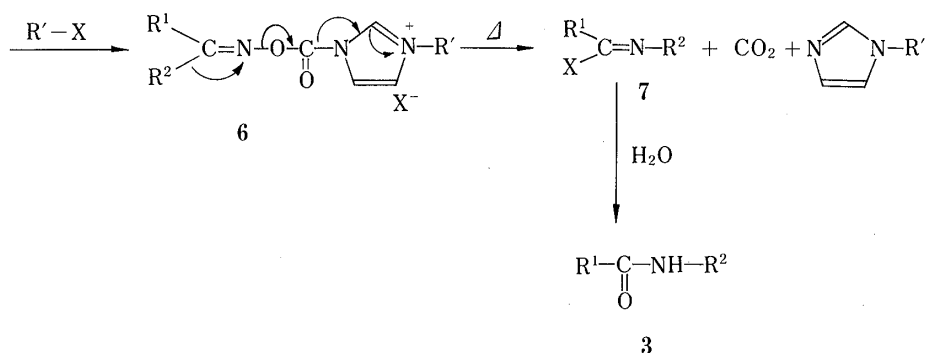
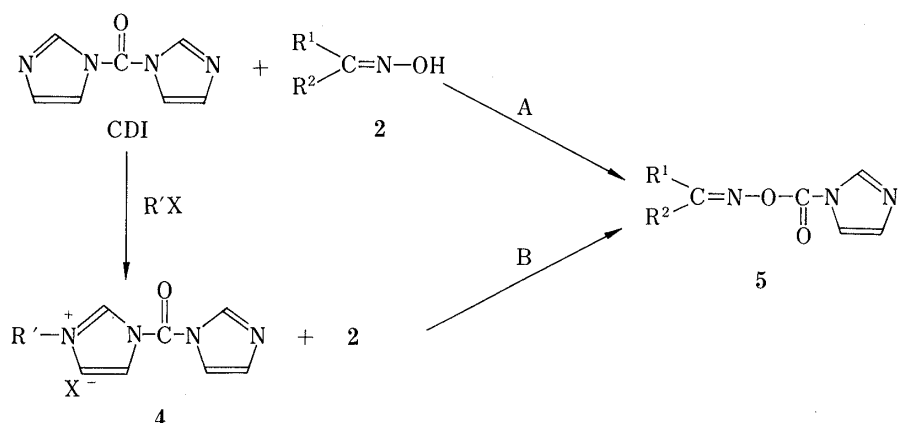


Chart 3

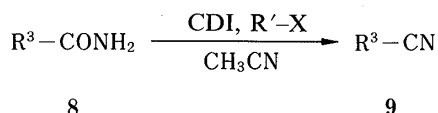


Chart 4

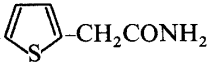

procedure is simple.

We observed the following features of this reaction: (a) the reaction of carboxamides (**8**) and CDI in the absence of $R'X$ does not give the products, (b) when equimolar amounts of CDI and $R'X$ with respect to the carboxamides (**8**) are used, the products are not the nitriles (**9**), but the carboxamides (**8**) (probably hydrolysis products of **10**) and 1-allylimidazole (**11**) (in the case where $R'X$ is allyl bromide), and (c) subsequent addition of excess $R'X$ gives the nitriles (**9**) in good yields.

From these results, the mechanism of this reaction is proposed to be as follows. First, CDI is activated by quaternization with $R'X$ to form the imidazolium salt (**4**). The salt (**4**) reacts with the carboxamide (**8**) to give the intermediate (**10**). Furthermore, quaternization of the imidazole ring of **10** with $R'X$ gives the active imidazolium salt (**12**). The oxycarbonylimidazolium moiety of **12** is easily cleaved with decarboxylation under heating to give the nitrile (**9**) (Chart 5). In this process, the quaternization of the imidazole ring with a reactive halide effectively promotes the reaction, that is, the imidazolium moiety of **4** and the oxycarbonylimidazolium moiety of **12** are efficient leaving groups.

Further applications of the oxycarbonylimidazolium moiety (**1**) as an efficient leaving

TABLE II. The Synthesis of Nitriles by the Dehydration of Primary Carboxamides

| Carboxamide 8 | Reaction condition ^{a)} | R'-X ^{b)} | Product 9 | Isolated yield (%) |
|---|----------------------------------|--------------------|--|---------------------|
| PhCH ₂ CONH ₂ | 2 h | A | PhCH ₂ CN | 9a ^{c)} 98 |
| MeOC(=O)-C ₆ H ₄ -CONH ₂ | 3 h | A | MeOC(=O)-C ₆ H ₄ -CN | 9b ^{c)} 93 |
| PhCH=CHCONH ₂ | 5 h | A | PhCH=CHCN | 9c ^{c)} 98 |
|  | 2 h | A |  | 9d ^{c)} 98 |
| Ph(CH ₂) ₃ CONH ₂ | 3 h | A | Ph(CH ₂) ₃ CN | 9e 96 |
| | 3 h | B | | 95 |

- a) Reflux time after stirring of the mixture for 0.5 h at room temperature.
 b) A: 2 eq of *N,N'*-carbonyldiimidazole and 8 eq of allyl bromide were used.
 B: 2 eq of *N,N'*-carbonyldiimidazole and 8 eq of benzyl bromide were used.
 c) These nitriles were identical in terms of IR and NMR spectra with authentic commercial samples.

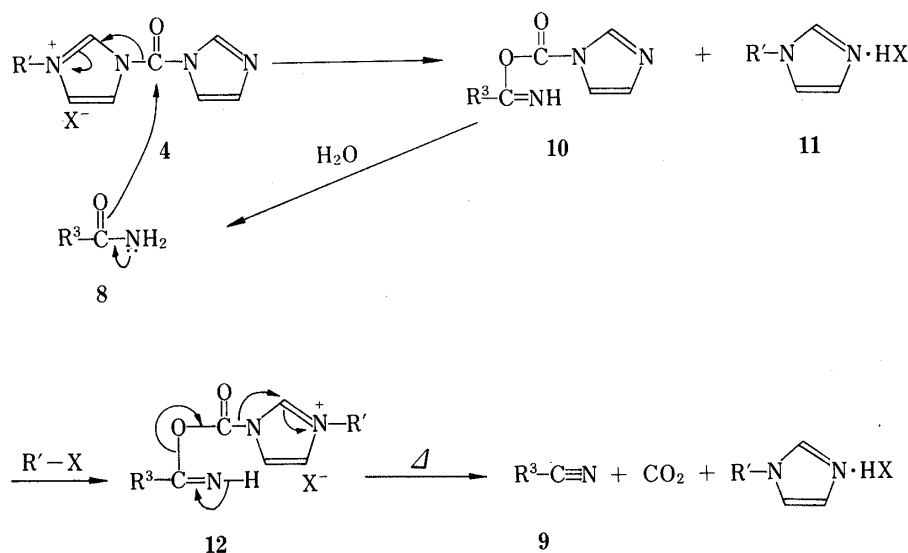


Chart 5

group in the other reactions are now being investigated.

Experimental

The infrared (IR) spectra were obtained with a Hitachi 260-10 infrared spectrophotometer. The nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-22 high-resolution nuclear magnetic resonance spectrometer in CDCl₃ or (CD₃)₂SO with Me₄Si as an internal standard. The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed with a Yanaco MT-2 CHN Corder.

General Procedure for Beckmann Rearrangement—A mixture of a ketoxime, *N,N'*-carbonyldiimidazole (1 eq), and a reactive halide (4–5 eq) in dry acetonitrile was refluxed for 0.5–1.5 h, and then treated with water. The mixture was concentrated and the residue was dissolved in ethyl acetate. This solution was washed with dil. HCl and aq. NaHCO₃, dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by recrystallization or column chromatography.

4-Methoxyacetanilide (3a)—Allyl bromide (2.42 g, 20 mmol) was added to a solution of 4-methoxyacet-

ophenone oxime (830 mg, 5 mmol) and *N,N'*-carbonyldiimidazole (815 mg, 5 mmol) in dry acetonitrile (10 ml), and the mixture was refluxed for 0.5 h. The reaction mixture was treated with water (10 ml) and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (60 ml) and the solution was washed with dil. HCl, aq. NaHCO₃, and water. The solution was dried (MgSO₄) and concentrated under reduced pressure. The residual solid was recrystallized from benzene-*n*-hexane to give 4-methoxyacetanilide (**3a**) (770 mg, 92.5%): mp 128–129 °C. IR (KBr): 3250 (NH), 1640 (C=O) cm⁻¹; ¹H-NMR (CDCl₃) δ: 2.02 (3H, s, CH₃CO), 3.68 (3H, s, CH₃O), 6.75 (2H, d, *J*=9 Hz, aromatic H), 7.34 (2H, d, *J*=9 Hz, aromatic H), 7.98 (1H, br s, amide H). *Anal.* Calcd for C₉H₁₁NO₂: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.24; H, 6.64; N, 8.41.

General Procedure for the Synthesis of Nitriles—A mixture of a carboxamide, *N,N'*-carbonyldiimidazole (2 eq), and a reactive halide (8 eq) in dry acetonitrile was stirred for 0.5 h at room temperature, and then refluxed for 2–5 h. The mixture was dissolved in ethyl acetate, and the solution was washed with dil. HCl and aq. NaHCO₃, then dried (MgSO₄), and concentrated under reduced pressure. The residue was purified by recrystallization or column chromatography.

4-Phenylbutyronitrile (9e)—Allyl bromide (1.9 g, 16 mmol) was added to a solution of 4-phenylbutyramide (326 mg, 2.0 mmol) and *N,N'*-carbonyldiimidazole (650 mg, 4.0 mmol) in dry acetonitrile (20 ml), and the mixture was stirred for 0.5 h at room temperature, and then refluxed for 5 h. The mixture was concentrated and the residue was treated as usual to give 4-phenylbutyronitrile (**9e**) (280 mg, 96%): colorless oil. IR (neat): 2240 (CN) cm⁻¹; ¹H-NMR (CDCl₃) δ: 1.92 (2H, q, CH₂), 2.24 (2H, t, CH₂), 2.72 (2H, t, CH₂), 7.0–7.45 (5H, m, aromatic H). *Anal.* Calcd for C₁₀H₁₁N: C, 82.71; H, 7.64; N, 9.65. Found: C, 82.51; H, 7.58; N, 9.40.

The compounds listed in Tables I and II were prepared by the same procedures.

References and Notes

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- 7) 4-Methoxyacetophenone-*O*-(1-imidazolylcarbonyl)oxime (**5a**): mp 129 °C (dec.). IR (KBr): 1760 (C=O) cm⁻¹; ¹H-NMR (CDCl₃) δ: 2.37 (3H, s, CH₃), 3.78 (3H, s, OCH₃), 6.90 (2H, d, *J*=9 Hz, aromatic H), 7.10 (1H, m, imidazole H), 7.46 (1H, m, imidazole H), 7.72 (2H, d, *J*=9 Hz, aromatic H), 8.20 (1H, m, imidazole H). *Anal.* Calcd for C₁₃H₁₃N₃O₃: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.15; H, 4.98; N, 16.36.