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# Beckmann reaction of oximes catalysed by chloral: mild and neutral procedures

Sosale Chandrasekhar* and Kovuru Gopalaiah

*Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India*

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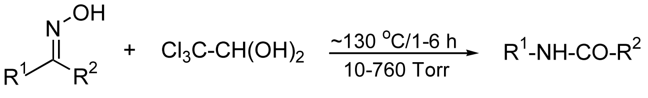
**Abstract**—A variety of ketoximes undergo the Beckmann rearrangement when heated with 0.5 molar equiv. of chloral (neat melt/~130°C), to furnish the corresponding amides in excellent yields (generally 80–95%) after simple work-up. (Aromatic aldoximes dehydrated to the corresponding nitriles in excellent yields under similar conditions.) The absence of solvent, Brønsted acids, strong Lewis acids and by-products, and a simple work-up characterise the procedures. © 2003 Elsevier Science Ltd. All rights reserved.

We have been interested in developing improved procedures for the historic Beckmann rearrangement in view of its continuing interest and importance.[1] We have recently reported several new procedures which are characterised by simplicity, mildness and environmental compatibility. We report herein another procedure for this important classical reaction which employs the readily available chloral as catalyst.

The search for improved conditions for the Beckmann reaction essentially involves a search for new electrophilic reagents with the desired characteristics of mildness, etc. (The reaction occurs under conditions of electrophilic activation of the oxime hydroxyl group.[1]) Generally, a variety of Brønsted and strong Lewis acids have been employed as reagents, e.g. *p*-toluenesulphonic acid, $SnCl_4$, $PCl_5$, etc. However, mild Lewis acids have hardly ever been reported to the best of our knowledge. It was of interest to investigate the possible use of chloral (trichloroacetaldehyde) in view of its ready availability and known Lewis acidic properties.[2] (The well-known fact that chloral generally exists as the hydrate derives from its highly electrophilic nature. In



**1** **2** **3**

**Scheme 1.** $R^1/R^2$ in **1**/**3**: (a) Ph/Me; (b) Ph/Et; (c) Ph/Ph; (d) 4-(MeO)$C_6H_4$/Me; (e) *p*-tolyl/Me; (f) 4-Cl$C_6H_4$/Me; (g) 4-Br$C_6H_4$/Me; (h) -$(CH_2)_5$-; (i) naphth-2-yl/Me.

**Table 1.** The conversion of the oximes **1**/**6** to the amides **3** or nitriles **7** with chloral: conditions and yields of the products (cf. Schemes 1 and 3)[a]

| Oxime | Conditions: °C/h | Amide/nitrile | Yield (%) |
|---|---|---|---|
| **1a** | 125/3 | **3a** | 95 |
| **1b** | 130/6 | **3b** | 74 |
| **1c** | 140/6.5 | **3c** | 84 |
| **1d** | 120/3.5 | **3d** | 98 |
| **1e** | 120/1.5 | **3e** | 97 |
| **1f** | 120/3.5 | **3f** | 89 |
| **1g** | 140/5 | **3g** | 85 |
| **1h** | 90/7.5 | **3h** | 67 |
| **1i** | 120/2.5 | **3i** | 89 |
| **6a** | 120/2 | **7a** | 87 |
| **6b** | 120/2.5 | **7b** | 73 |
| **6c** | 140/2.5 | **7c** | 94 |
| **6d** | 135/4.5 | **7d** | 96 |

[a] *Typical procedure*. An intimate mixture of the oxime (1.0 mmol) and chloral hydrate (0.5 mmol) was heated, first in vacuo (10 Torr) for 0.5 h and then at 760 Torr under $N_2$ as indicated (Table 1). The mixture was taken into $CH_2Cl_2$, washed with water and worked-up in the usual way.[1] The crude products were recrystallised (EtOAc/ligroin) the resulting pure compounds being identified by their mp's and spectral data (IR, 300 MHz $^1$H NMR and mass spectra). Note that in the case of cyclohexanone oxime **1h**, and of the aldoximes **6** generally, pre-formed chloral (obtained by heating the hydrate at 110°C/0.5 Torr/1 h) was employed to avoid hydrolysis.

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*Keywords*: Beckmann rearrangement; catalytic; chloral; environmentally mild.

* Corresponding author. Fax: (+91 80) 3600 529; e-mail: sosale@orgchem.iisc.ernet.in

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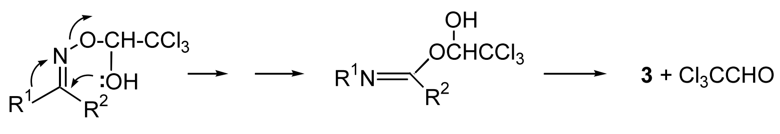

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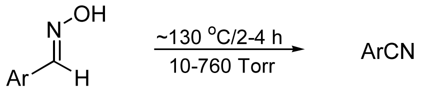
Scheme 2.

the present studies chloral was generated in situ by heating the hydrate in vacuo.)

When a variety of ketoximes **1** was admixed with chloral hydrate **2** (0.5 molar equiv.) and the mixture heated (initially at 10 Torr and then under $N_2$) the Beckmann rearrangement was effected in excellent yields to afford the expected amides **3** (Scheme 1, Table 1). It is possible that the mechanism (Scheme 2) involves initial formation of the hemi-acetal intermediate **4** which breaks down to **5** via nucleophilic participation of the hydroxyl group as shown;[1] **5** breaks down to the amide **3**, regenerating chloral in the process and enabling an overall catalytic process. A few aromatic aldoximes **6** were also investigated, and were found to undergo dehydration to the corresponding nitriles **7** in good yields under the above conditions (Table 1, Scheme 3; the oximes **1** and **6** had the indicated stereochemistry.)

The above reactions could also be effected by heating the oximes with chloral, which had been pre-formed from the hydrate as above: and in these cases the reactions were complete with less than 0.5 molar equiv. of chloral. Also, the initial in vacuo phase was essential as otherwise partial hydrolysis of the oximes was observed, presumably by the water in chloral hydrate. Thus, by all indications the active reagent species is chloral, formed by heating the hydrate in vacuo. (This is easily removed by washing the reaction mixture with water.)



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7

Scheme 3. Ar in **6**/**7**: (a) *p*-anisyl; (b) 3-MeO-4-(OH)$C_6H_3$; (c) 3,4-$(MeO)_2C_6H_3$; (d) naphth-1-yl.

Although chloral is known to participate in aromatic electrophilic substitution reactions, it is generally a weaker electrophile than the metal halides ($SnCl_4$, etc.).[2] Chloral is less toxic than most other reagents for the Beckmann reaction, the hydrate having found use as a sedative in the past.[3] It is also inexpensive, easily stored and effective catalytically. Thus, the Beckmann rearrangement has been effected under neutral, relatively mild and solvent-free conditions with an exceedingly simple work-up, all of which make it environmentally mild.

## References

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