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Beckmann rearrangement in the solid state: reaction of oxime hydrochlorides

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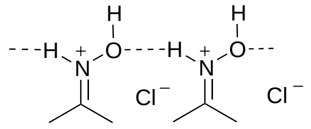
Abstract—Several ketoxime hydrochlorides undergo Beckmann rearrangement upon heating below their melting points for 5–48 h, in excellent yields (generally >70%). The absence of a reaction solvent and of by-products (except for HCl) makes for a very simple work-up. Aldoxime hydrochlorides apparently undergo dehydration to the corresponding nitriles under the above conditions. Dibenzyl ketoxime hydrochloride unexpectedly furnished a pyrazine derivative (67%), presumably via further reaction of the intermediate nitrilium ion in the crystal lattice. © 2001 Elsevier Science Ltd. All rights reserved.

The age-old Beckmann rearrangement remains of prime synthetic importance even today, essentially because it allows easy access to a variety of *N*-substituted carboxylic amides. We have recently reported improved procedures for the reaction,[1] and herein report a solid state version of the reaction.

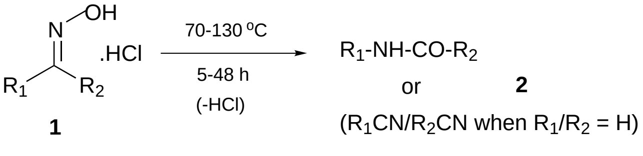
An important feature of the Beckmann reaction is that it is a rearrangement, so that no additional reagents—apart from a catalyst—are in principle required. Essentially dehydrating conditions have previously been employed for the reaction, in order to generate the intermediate nitrilium species without hydrolysing the oxime function. However, these requirements may also be met by employing appropriate acid catalysts in organic solvents—a solution of dry hydrogen chloride in ether thus seemed appropriate.

Treating ether solutions of several ketoximes with dry hydrogen chloride gas to saturation at 0–25°C, generally furnished a precipitate without any evidence of rearrangement (TLC). The precipitates were difficult to isolate as they were hygroscopic, and hence were tentatively identified as the oxime hydrochlorides. Removal of the ether in vacuo furnished the hydrochlorides as dry powders, the melting points of which could be determined by careful handling under nitrogen.

We then surmised that the above hydrochlorides would undergo Beckmann reaction in the crystalline lattice because of the electrophilic activation provided by the hydrogen chloride—presumably hydrogen bonded to the oxygen and nitrogen atoms in the lattice network (Scheme 1). The reaction was indeed observed by heating the hydrochlorides of a variety of ketoximes (**1**), at temperatures ~20°C below their melting points for periods ranging from 5 to 48 h under nitrogen (Scheme 2 and Table 1; the white solid hydrochlorides often darkened during the progress of the reaction, but did not melt). The amide products **2** were isolated and characterised by their physical constants and spectra (IR and NMR).[†] The stereochemistry of the oximes studied is presumed to be as in **1**, as indicated by the



Scheme 1.



Scheme 2.

Keywords: Beckmann; nitrile ylide; oxime hydrochlorides; pyrazine; rearrangement; solid state.

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Table 1. Beckmann rearrangement of solid ketoxime hydrochlorides (**1**·HCl) to amides/lactams **2**: melting points of **1**·HCl, reaction conditions and yields of **2**

R_1	R_2	**1**·HCl	Mp (°C)	(°C)/h[a]	**2**	Yield (%)
Ph	Ph	**a**	125–128	105/8	**a**	96
Ph	Me	**b**	108–110	85/16	**b**	83
p-Tolyl	Me	**c**	120–122	105/15	**c**	90
$-(CH_2)_5-$		**d**	85–87	70/48	**d**	72[b]
Vanillin		**e**	135–137	100/8	**e**	92[c]
1-Naphthaldehyde		**f**	108–110	90/12	**f**	78[d]
$PhCH_2$	$PhCH_2$	**g**	140–141	110/20	**g**	67[e]
(+)-Camphor		**h**	148–150	130/5	**h**	~60[f]

[a] Reaction conditions (temperature/hours).

[b] Caprolactam from cyclohexanone oxime hydrochloride.

[c] 4-Hydroxy-3-methoxybenzonitrile.

[d] 1-Naphthonitrile.

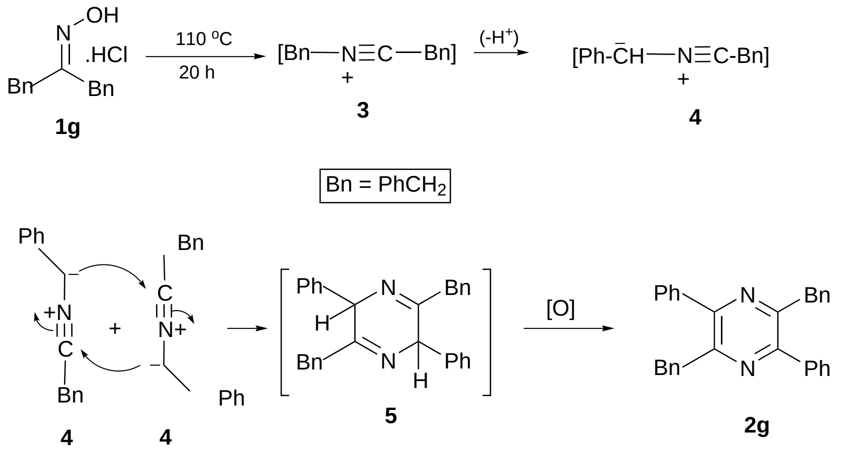
[e] 2,5-Dibenzyl-3,6-diphenylpyrazine identified by elemental analysis and comparison with reported data:[2] mp 152–153°C (lit.[2a] 151–153°C); ν_{max} (KBr) 3081, 1600 cm^{-1}; λ_{max}^{MeOH} (log ε) 247 (3.89), 297 (3.86) nm; δ_H (300 MHz, $CDCl_3$) 4.27 (s, 4H, 2×PhCH_2), 7.10–7.25 (m, 10H, Ar*H*), 7.43–7.53 (m, 10H, Ar*H*); δ_C (125 MHz, $CDCl_3$) 41.15, 126.64, 128.76, 128.80, 129.08, 129.27, 129.68, 139.04, 139.67, 150.51, 152.32; m/e 412 (M^+), 411.

[f] Complex mixture indicating fragmentation to nitriles.[3]

solution phase Beckmann reaction:[1] the present results thus also indicate the migration of the group *anti* to the oxime hydroxyl group.

The oxime hydrochlorides of vanillin (**1e**) and 1-naphthaldehyde (**1f**) dehydrated to the corresponding nitriles (**2e** and **2f**, respectively) in good yields under the above conditions. Dibenzyl ketoxime hydrochloride furnished what is apparently 2,5-dibenzyl-3,6-diphenylpyrazine (**2g**):[2] this may form via the dimerisation of the nitrile ylide (**4**) obtained by the deprotonation of the nitrilium species (**3**) initially formed upon rearrangement, and the oxidation of the resulting dihydropyrazine **5** most likely during work-up (Scheme 3). This sequence of events indicates the power of the solid state method in effecting unusual transformations, under the control of the crystal lattice.

The oxime hydrochloride of (+)-camphor furnished a complex mixture of products when subjected to the above conditions. IR and NMR spectra indicated the presence of nitriles: the fragmentation of camphor oxime to nitriles under Beckmann conditions is well known,[3] and the above mixture was not analysed further.



Scheme 3.

[†] Typical procedure: A stirred solution of the oxime **1** (1 g) in dry diethyl ether (20 ml), in a 100 ml two-necked round-bottomed flask protected by a $CaCl_2$ guard tube, was saturated with dry hydrogen chloride gas via an inlet. A white solid precipitated out, which was allowed to settle and collected by pipetting out the supernatant ether under nitrogen, and removing trace volatiles in vacuo. A pinch was transferred under nitrogen to a melting point capillary, which was then fully sealed before the determination of the mp. The rest was heated under nitrogen as indicated (Table 1), the reaction being followed by TLC. The darkened solid was cooled and taken into ether; the resulting solution was washed successively with $NaHCO_3$ solution and water, dried ($MgSO_4$) and the solvent evaporated in vacuo. The products **2** were purified by recrystallisation and identified by their mp's, and IR and ^1H NMR spectra.

The present method employs no solvent in the rearrangement step per se and the work-up is simple—washing an ether solution of the reaction mixture with bicarbonate solution to remove the hydrogen chloride, etc. The absence of by-products also adds to the overall simplicity of the procedure. There are two previous reports of the solid-state Beckmann reaction,[‡] involving the oxime picrates[4] and the admixing of oximes and *p*-toluenesulphonic acid.[5] However, the present method is apparently advantageous as it employs the simple and inexpensive hydrogen chloride.

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[‡] We are grateful to a referee for kindly bringing these to our attention.