Pergamon

Tetrahedron Letters 43 (2002) 2455–2457

TETRAHEDRON LETTERS

Beckmann rearrangement of ketoximes on solid metaboric acid: a simple and effective procedure

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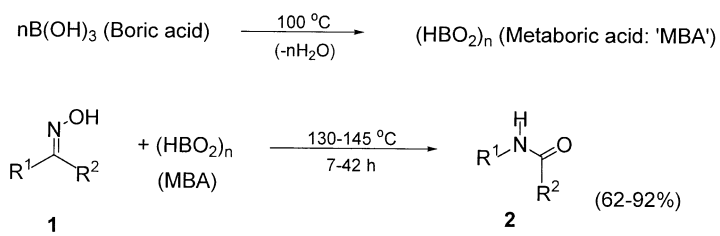
Received 19 December 2001; revised 23 January 2002; accepted 6 February 2002

Abstract—When ketoximes admixed with solid metaboric acid (formed from boric acid at 100°C/0.1 Torr) are heated (~140°C/7–42 h), the corresponding amides or lactams are produced in excellent yields (62–92%) via the Beckmann reaction. Aromatic aldoximes undergo both dehydration to the nitrile as well as (non-stereospecific) rearrangement under the above conditions. The absence of solvent, and the mildness and low toxicity of boric acid, characterise the present procedure.

We have recently reported several improved versions of the Beckmann rearrangement in view of the continuing general interest in this classical synthetic procedure.[1] The study of the reaction is greatly aided by the simple and well-established mechanism, but this also implies that new variants must be unusually novel to be useful. An enormous variety of reaction conditions have been reported over the century or so since the reaction was first discovered, although few of them would meet the sophisticated requirements of the present day, which lay stress on mildness and environmental concerns.

We were attracted to the possible use of boric acid for effecting the Beckmann reaction by its mildness (pK_a 9.25)[2] and low mammalian toxicity (it has been employed as a bacteriacidal in eyewashes, skin creams, etc.).[3,4] Also, borate species are known to add water reversibly,[2] a characteristic relevant to the Beckmann reaction, which may be viewed as a dehydration–rehydration sequence effected on the protonated oxime. (Boric acid has found occasional use in organic synthesis.[5])

Initial studies indicated that oximes were unreactive towards a suspension of boric acid in organic solvents. However, when the oximes were directly absorbed on boric acid and the solid mass heated (without a solvent) above 100°C, the expected rearrangement was observed, but with competing hydrolysis of the oximes. Also, droplets of (presumably) water were observed in the reaction flask, and there was no reaction at lower temperatures. All this apparently indicated that the boric acid was being converted under the reaction conditions to metaboric acid ('MBA', Scheme 1), which was presumably the active species effecting the rearrangement, and that the liberated water was responsible for the competing hydrolysis. (Boric acid is known to dehydrate sequentially >100°C to yield initially metaboric acid and finally boric anhydride).[2–5] It was clear that pre-formed metaboric acid would avoid the hydrolysis and lead exclusively to the Beckmann rearrangement and this was indeed confirmed in the event: several ketoximes upon admixture with metaboric acid and heating furnished the expected amides or lactams



Scheme 1.

Keywords: Beckmann; boric acid; formanilide; metaboric acid; rearrangement; solid state.
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0040-4039/02/$ - see front matter
PII: S0040-4039(02)00282-4

in excellent yields (Scheme 1 and Table 1; note that 'MBA' is oligomeric[2]).† The stereochemistry of the ketoximes studied is presumed to be that depicted (Scheme 1 and Table 1) based on their Beckmann rearrangement in solution, the usual *anti* migration pathway thus being observed.

The reaction of aromatic aldoximes with 'MBA' apparently gave both the products of dehydration (the nitriles) and those of the Beckmann rearrangement as complex mixtures, as indicated by IR, NMR and GC–MS (Scheme 2, Table 1). The mixtures were not separated and the stereochemistry of the rearrangement was not ascertained, but the presence of multiple carboxamide bands in the IR ($\sim$1650 cm^{-1})[6] indicated low selectivity. (This was supported by the GC–MS results: indeed, Beckmann rearrangement of aldoximes is generally non-stereospecific, essentially because of competing stereoisomerisation of the oxime.[7])

A likely mechanism for the above transformation involves the intermediacy of the metaborate ester **7** of the oxime, presumably formed via the ate-complex adduct **6** (Scheme 3, the oligomeric form of 'MBA'

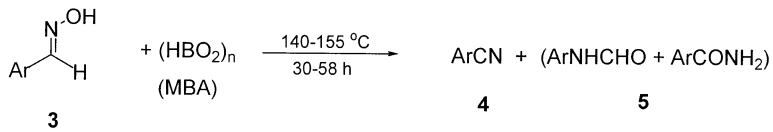
Table 1. Reaction of the ketoximes **1** (Scheme 1) and aldoximes **3** (Scheme 2) with metaboric acid: reaction conditions, products and yields

	Oxime		Reaction conditions (°C/h)	Product(s)	Yield (%)
1/**3**	R^1	R^2			
1a	Ph	Ph	140–145/17	**2a**	92
1b	Ph	Me	140–145/20	**2b**	85
1c	*p*-Tolyl	Me	130–135/16	**2c**	87
1d	-$(CH_2)_5$-		135–140/42	**2d**[a]	62
1e	(+)-Camphor		135–140/7	Mixture[b]	90[b]
3a	3,4-$(OMe)_2C_6H_3$-	H	151–155/30	**4a**+**5a**[c]	84
3b	4-$(OMe)C_6H_4$-	H	140–145/46	**4b**+**5b**[c]	78
3c	Naphth-1-yl	H	150–155/58	**4c**+**5c**[c]	65

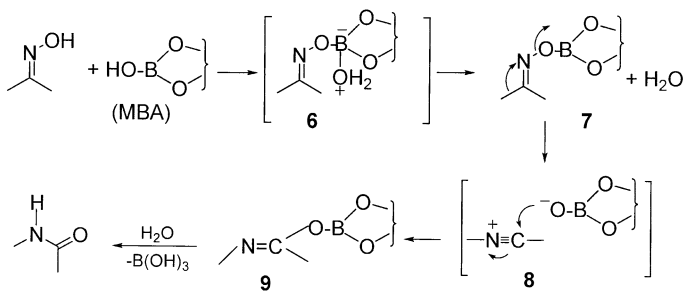
[a] *ε*-Caprolactam.

[b] This consisted of a nitrile (1.0 part) and possibly a δ-lactam (1.4 parts) as seen by IR and GC–MS [ν_{max} (neat/cm^{-1}) 2246 and 1663, M^+ 149 and 167, for the nitrile and the lactam, respectively): the fragmentation of camphor oxime to nitriles[8] as also the formation of a δ-lactam[9] under Beckmann reaction conditions is known, and the mixture was not analysed further.

[c] **4a**:**5a** = 1.0:1.9, **4b**:**5b** = 1.0:0.6, **4c**:**5c** = 1.0:2.5 (ratios by GC–MS: M^+ was observed in all the cases, and amides **5** were $\sim$1:3 mixtures of the two possible isomers); ν_{max} (neat/cm^{-1}) $\sim$2222 cm^{-1} (CN), 1648–1668 (amide I).[6]



Scheme 2.



Scheme 3.

† Typical procedures: Boric acid was converted to metaboric acid[3] by heating at 110–115°C/0.1 Torr over P_2O_5 for 4 h. The oxime (1 mmol) and the metaboric acid (3 mmol) were ground together using a pestle and mortar under a blanket of N_2, the resulting solid mixture was placed in a round-bottomed flask under N_2 and heated under the conditions shown in Table 1. The reaction was followed by TLC and upon completion the solid mixture was taken in $CHCl_3$ and the resulting suspension washed with water. The organic part was dried ($MgSO_4$) and the solvent evaporated in vacuo. The products in the case of the ketoximes **1a**–**1d** were purified by crystallisation (EtOAc–ligroin), and identified by their melting points and spectra (IR, 300 MHz ^{1}H NMR and MS). In the case of camphor oxime **1e** and the aromatic aldoximes **3**, the reaction mixtures were analysed by GC–MS to give the product ratios, followed by IR and 300 MHz ^{1}H NMR which indicated the presence of the reported products.

containing B_3O_3 rings[2] is partially represented). The activated ester **7** undergoes Beckmann rearrangement, the resulting incipient nitrilium ion **8** being recaptured by the metaborate counterion at the carbon atom to form the imino-metaborate **9**, which is hydrolysed to the final amide/lactam upon work-up. (Alternatively, **8** may also react with the water produced during the formation of **7**; in either case, boric acid is presumed to be the final by-product after work up. Also, although 'MBA' apparently plays a catalytic role, a minimum of 3 molar equivalents of it vis-a-vis the oxime was found to be required in practice.)

There are two previous reports of the Beckmann rearrangement having been effected by boric acid or its anhydrides, both involving the high temperature conversion of cyclohexanone oxime to caprolactam with either boric acid in a solvent (e.g. tetralin)[10] or B_2O_3 on a reactor bed[11] (optimally at 600 K);‡ interestingly in the latter case, a role for metaboric acid was indicated by the need for a small amount of water to be present. The present procedure employs relatively low temperatures and no solvent; the simple formation of the reagent (metaboric acid) from the inexpensive boric acid, the exceedingly simple work-up and the fact that the boric acid by-product is relatively harmless are also noteworthy. Thus, simplicity and low toxicity mark the present procedure.

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

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