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Solid phase synthesis of amides by the Beckmann rearrangement of ketoxime carbonates

Sarah His,[a] Christophe Meyer,[a] Janine Cossy,[a,]* Gibert Emeric[b] and Alfred Greiner[b]

[a]*Laboratoire de Chimie Organique, associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France*
[b]*Bayer Cropscience SA, La Dargoire Research Center, 14-20 rue Pierre Baizet, BP 9163, Lyon Cedex 09, France*

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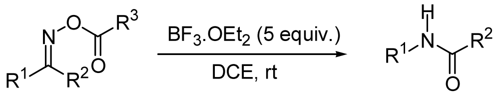
This paper is dedicated to the memory of the late Sarah His

Abstract—In the presence of trifluoroacetic acid, ketoxime benzyl carbonates undergo a Beckmann rearrangement to the corresponding amides. This reaction was translated to a solid support by immobilizing oximes in the form of mixed carbonates derived from hydroxymethylpolystyrene in order to produce a diversity of amides with high efficiency.

Combinatorial chemistry has become a powerful tool for the rapid development of novel lead compounds and optimization of their therapeutic efficiency. In this context, impressive efforts have been devoted to transfer techniques and reactions originally tuned-up in liquid phase to solid support with the ultimate goal of performing the widest array of transformations in solid phase synthesis.[1] The Beckmann rearrangement involving the transformation of ketoximes into amides is a fundamental reaction in organic synthesis, and has led to numerous applications due to the ease with which nitrogen can be inserted into carbon chains starting from readily available ketones.[2] Herein, we would like to report our results related to the development of a version of the Beckmann rearrangement on solid support with the aim of converting a wide variety of ketoximes to the corresponding amides with high efficiency.

The Beckmann rearrangement is usually promoted by strong protic or Lewis acids[2] and its practical importance has led to the development of improved or catalytic variants based on milder and/or environmentally benign conditions.[3–11] The role of the different promotors with respect to the mechanism of the Beckmann rearrangement, is to transform the hydroxyl group of the ketoximes into a better nucleofuge and induce the concomitant migration of the organic group usually at the *anti* position.[2] Therefore, the possibility of attaching oximes to solid support by their oxygen atom in the form of a suitably chosen oxime derivative, which could act as an activating group for the Beckmann rearrangement, appeared particularly attractive. A brief screening first indicated that the benzyl ethers of various ketoximes were not viable precursors since their Beckmann rearrangement failed to occur under various reaction conditions (protic or Lewis acids). The behaviour of oxime esters was then investigated, and acetophenone oxime benzoate **1** and benzophenone oxime *p*-methoxybenzoate **2** could indeed be rearranged to acetanilide **4a** (60%) and benzanilide **4b** (70%), respectively, by using a large excess of $BF_3{\cdot}OEt_2$ (5 equiv.) in 1,2-dichloroethane (DCE) at room temperature.[12] Unfortunately, the Beckmann rearrangement of cyclohexanone oxime benzoate **3** under the same conditions was extremely sluggish and ε-caprolactam **4c** was obtained in only 25% yield (Scheme 1).

These results led us to consider the behaviour of the oxime carbonates which were anticipated to exhibit higher reactivity.[13,14] It was reported that $BF_3{\cdot}OEt_2$ was



1 R^1 = Me, R^2 = Ph, R^3 = Ph — **4a** 60%
2 R^1 = R^2 = Ph, R^3 = *p*-MeO-Ph — **4b** 70%
3 R^1,R^2 = $-(CH_2)_5-$, R^3 = Ph — **4c** 25%

Scheme 1. Beckmann rearrangement of oxime benzoates.

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* Corresponding author. Tel.: +33-1-40-79-44-29; fax: +33-1-40-79-46-60; e-mail: janine.cossy@espci.fr

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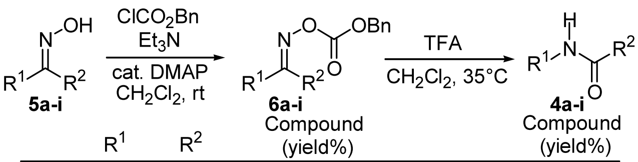
successful at promoting the Beckmann rearrangement of various ketoxime ethyl carbonates,[3a] and for our part, we studied the Beckmann rearrangement of benzyl carbonates in liquid phase with the aim of performing this rearrangement on solid support by using a resin having an activated acyl carbonate anchoring moiety, derived from benzylic alcohol type resins (hydroxymethylpolystyrene or Wang resin). A series of ketoximes **5a**–**i** were converted to their benzyl carbonates **6a**–**i** (BnOCOCl, Et_3N, cat. DMAP, CH_2Cl_2, rt) and it was demonstrated that these compounds underwent a Beckmann rearrangement when treated with a trifluoroacetic acid/dichloromethane mixture (9/1 to 1/1) at 30–35°C, affording the corresponding amides **4a**–**i** in satisfactory yields (Table 1).

According to literature precedents[13] and our observations, the greater ability of ketoxime carbonates to undergo the Beckmann rearrangement was attributed to the thermodynamically favorable (and detectable) evolution of carbon dioxide, and not the assistance by the carbonyl group of the carbonate moiety as recently suggested.[3a] The rearrangement is therefore accompanied by the release of benzyl alcohol and the formation of the labile iminol trifluoroacetates **7a**–**i**, whose subsequent hydrolysis generates the corresponding amides **4a**–**i**. It is noteworthy that oximes **5a**–**i** were stable under the reaction conditions (TFA), thus highlighting the fact that the carbonates were the actual reactive species and not the oximes themselves which could have been generated by an acid-catalyzed hydrolysis (Scheme 2).

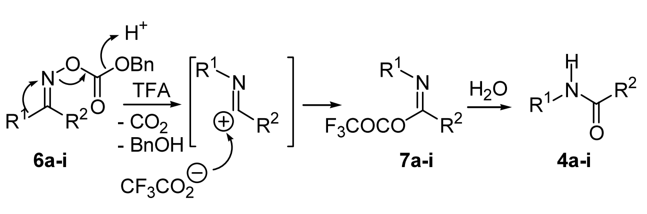
The translation of this sequence to solid support was next investigated. In order to immobilize ketones in the form of mixed carbonates, several resins bearing an activated acyl moiety were synthesized. Thus, the Wang resin **8** or hydroxymethylpolystyrene **9** (cross-linked polymers with 1% of divinylbenzene) were converted to the *p*-nitrophenylcarbonate resins **10** and **11** respectively by treatment with *p*-nitrophenylchloroformate in the presence of *N*-methylmorpholine in dichloromethane at room temperature.[14] On the other hand, hydroxymethylpolystyrene **9** was converted to the acylimidazole resin **12** by treatment with carbonyldiimidazole in THF at room temperature (Scheme 3).[15]

Table 1. Preparation and Beckmann rearrangement of ketoxime benzyl carbonates

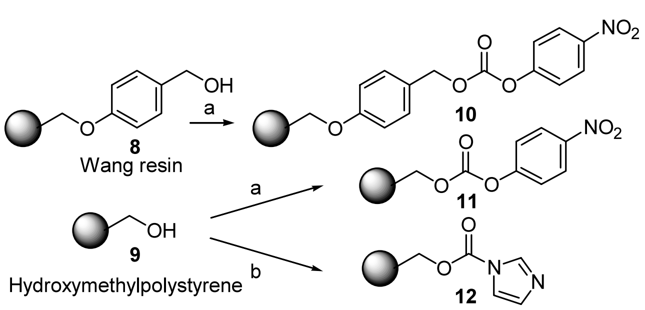


	R^1	R^2	Compound (yield%)	Compound (yield%)
5a	Ph	Me	**6a** (80)	**4a** (60)
5b	Ph	Ph	**6b** (85)	**4b** (75)
5c	-$(CH_2)_5$-		**6c** (80)	**4c** (60)
5d	*p*-I-C_6H_4	Me	**6d** (75)	**4d** (63)
5e	*p*-Ph-C_6H_4	Me	**6e** (53)	**4e** (56)
5f	*p*-Me-C_6H_4	Et	**6f** (48)	**4f** (70)
5g	*p*-Br-C_6H_4	Et	**6g** (52)	**4g** (85)
5h	*n*-Bu	*n*-Bu	**6h** (65)	**4h** (70)
5i	Bn	Bn	**6i** (45)	**4i** (94)

The ketoximes **5a**–**i** were loaded on the resins **10**–**12** under optimized conditions involving heating in DCE at 60°C for 72 h.[16] The resulting ketoxime carbonate resins of type **A** and **B** were then treated with a TFA/CH_2Cl_2 (9/1) mixture at 35°C for 16 h and the products were cleaved from the resins and analyzed by NMR and GC–MS. The results are summarized in Table 2 and the yields reported refer to the initial loadings of the commercially available resins **8** and **9**.[17]

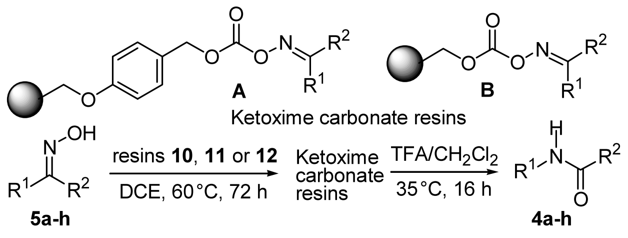


Scheme 2. Mechanism of the Beckmann rearrangement of ketoxime carbonates in the presence of TFA.



Scheme 3. Preparation of resins **10**–**12**. *Reagents and conditions*: (a) *p*-nitrophenylchloroformate, *N*-methylmorpholine, CH_2Cl_2, rt, 18 h; (b) carbonyldiimidazole, THF, rt, 3 h.

Table 2. Beckmann rearrangement of ketoxime carbonates on solid support



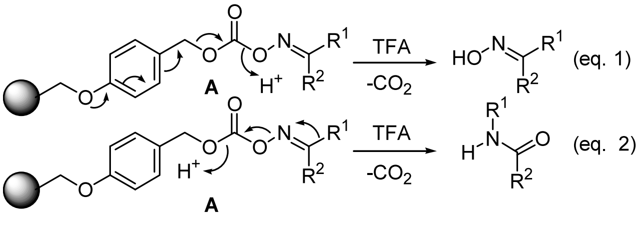
Oximes	R^1	R^2	Resin	Resin type	Amides **4** (yield%)
5a	Ph	Me	**10**	**A**	**4a** (60)
			11	**B**	**4a** (75)
			12	**B**	**4a** (65)
5b	Ph	Ph	**12**	**B**	**4b** (95)
5c	-$(CH_2)_5$-		**10**	**A**	oxime **5c** recovered
			11	**B**	**4c** (90)
			12	**B**	**4c** (85)
5d	*p*-I-C_6H_4	Me	**12**	**B**	**4d** (85)
5e	*p*-Ph-C_6H_4	Me	**12**	**B**	**4e** (95)
5f	*p*-Me-C_6H_4	Et	**12**	**B**	**4f** (95)
5g	*p*-Br-C_6H_4	Et	**12**	**B**	**4g** (73)
5h	*n*-Bu	*n*-Bu	**12**	**B**	**4h** (51)

The overall sequence was first investigated with two representative oximes **5a** and **5c**, respectively, derived from acetophenone and cyclohexanone. Whatever the resin used to immobilize the ketoxime **5a**, acetanilide **4a** was obtained in satisfactory yields (60–75%). By contrast, in the case of cyclohexanone oxime **5c**, ε-caprolactam **4c** was obtained in high yield when resins **11** and **12** derived from hydroxymethylpolystyrene were used for the loading, whereas oxime **5c** was the only product recovered when resin **10** was used. The difference between both cases could be explained by the presence of the *p*-anisyl spacer in resins of type **A** derived from the Wang resin, which could induce the direct cleavage of ketoximes from the solid support (Eq. (1)) and compete with the Beckmann rearrangement (Eq. (2)) if the latter occurred at a much slower rate, which was indeed anticipated to be the case for cyclohexanone oxime compared to acetophenone oxime derivatives (Scheme 4).

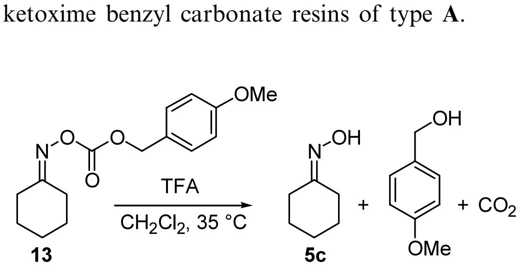
This result was further confirmed in liquid phase by the fact that the *p*-methoxybenzyl carbonate **13** derived from cyclohexanone oxime quantitatively reverted to oxime **5c** upon treatment with TFA, whereas the benzyl carbonate **6c** rearranged to ε-caprolactam **4c** under the same conditions (Scheme 5, Table 1).

This side reaction was therefore suppressed by using resins **11** and **12** prepared from hydroxymethylpolystyrene lacking the *p*-anisyl spacer and amides **4a**–**h** were obtained in good yields by the Beckmann rearrangement of ketoxime carbonates of type **B** (Table 2).

In summary, we have described a version of the Beckmann rearrangement on solid support involving the immobilization of ketoximes in the form of oxime carbonates and their subsequent reaction with trifluoroacetic acid, which releases the corresponding amides in solution. The overall sequence, which affords in most cases the amides in good yields and in a high state of purity, may find applications in solid phase synthesis.



Scheme 4. Beckmann rearrangement versus direct cleavage with ketoxime benzyl carbonate resins of type **A**.



Scheme 5. Reactivity of the *p*-methoxybenzyl carbonate of cyclohexanone oxime.

Acknowledgements

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