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ABSTRACT

A facile and efficient procedure is developed for one-pot synthesis of amides from ketones in the presence of P_2O_5/SiO_2 reagent in dry media under microwave irradiation. Ketoximes indirectly in the same conditions gave amides by Beckmann rearrangement.

Key Words: Amides; Ketones; Ketoximes; Beckmann type rearrangement; Microwave irradiation; P₂O₅/SiO₂.

The Beckmann rearrangement of ketoximes has been used extensively in organic synthesis^[1] due to the simplicity at which the reaction

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affects nitrogen insertion into a carbon framework and the fact that the rearrangement is usually stereospecific. Several methods for this rearrangement have been reported in the literature that include the use of formic acid,^[2] liquid SO₂, HMPA,^[3] SOCl₂,^[4] silica gel,^[5] P₂O₅-methanesulfonic acid,^[6] HCl-HOAc, Ac₂O,^[7] polyphosphoric acid,^[8] AlCl₃,^[9] BiCl₃,^[10] and rhodium complex.^[11]

On the other hand, chemical methods^[12] for the synthesis of oximes usually give a mixture of the two geometrical isomers, which must be separated by chromatography or recrystallization techniques. However, the reagents that have been used for oximation of ketones or Beckmann rearrangement, also catalyze interconversion of this geometrical isomers.^[13] The stereochemistry of oxime in some cases are unimportant and the mixture of products (one major) were obtained in Beckmann rearrangement.^[9,11] As a result there is always considerable interest in finding more selective methods of oxime synthesis or direct pathways.

Very few methods are available for direct amidation of ketones.^[14–17] Methods for simultaneous oximation of ketones and rearrangement to the amides, in the case of cyclohexanone are known in the literature, either with the use of hydroxylamine and sulfuric acid,^[14] or by employing primary nitroparaffines as a source of hydroxylamine.^[15] In the former case, generally large excess of concentrated sulfuric acids is required, which subsequently must be neutralized. This process is, thus, unattractive in many cases, particularly in systems, which are sensitive to sulfuric acid, as well as because of the required work up. In 1979, G. Olah^[16] reported a one-step conversion of alicyclic ketones into lactams with hydroxylamine-O-sulfonic acid and formic acid under reflux condition. Interestingly it was observed^[17] that when this reaction was carried out over SiO₂ under microwave irradiation, it gives an amino acid salt, which cyclizes to the corresponding lactam after work up in basic medium. But most of these have some disadvantages in relation to their general applicability, selectivity, availability, operational convenience, and toxicity.

Our project has been continually working on the basis of developing of new synthetic methods using P_2O_5/SiO_2 in solid phase.^[18] Having the above facts in mind, we wish to report a very simple and efficient method for one-pot synthesis of amides from ketones using the P_2O_5/SiO_2 reagent in solid phase under microwave irradiation.

In an attempt to examine the Lewis acid property of P_2O_5/SiO_2 in the solid state, 2 mmol of cyclohexanone and 4 mmol of hydroxylamine hydrochloride were mixed with 1 g of P_2O_5/SiO_2 reagent in an agate mortar, and then the uniform mixture was irradiated by microwave for

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 $\begin{array}{c} R \\ R' \end{array} \longrightarrow O + HONH_2 .HCl \\ \hline P_2O_5 / SiO_2 \\ \hline MW, 2-8 \text{ min.} \end{array} RCONHR' + R'CONHR \\ \end{array}$



5 min. ε -Caprolactam was obtained instead of cyclohexanone oxime, in 88% yield, which can be used in manufacture of polyamides such as Nylon 6.^[16]

In order to prepare amides, various types of ketones were mixed with hydroxylamine hydrochloride in the presence of P_2O_5/SiO_2 reagent using microwave irradiation in solid phase. In this approach, amides were obtained instead of oximes. In the absence of microwave irradiation, after 15 min grinding of mixture the starting material was recovered whereas aldehydes give corresponding oximes in the same conditions.^[18b] The general reaction is illustrated according to the Sch. 1 and the results have been reported in Table 1. All reactions were performed in less than 8 min. As shown in the Table 1 several structurally varied ketones underwent cleans, remarkably fast and direct nitrogen insertion reactions by a Beckmann type rearrangement to the corresponding amides. This mild and versatile method can also be applied for both aromatic and aliphatic ketones.

Although the mechanism of this transformation is not clear, the first step is probably the addition–elimination reaction of hydroxylamine hydrochloride and formation of an oxime-phosphate intermediate. In the second step, the conversion should take place by the migration of one of the alkyl or aryl group. Usually one of the isomeric product is predominate, which is the one that more bulky group has migrates (Entries 3–6, 8, 9). In the Entry 7 only the methylene migration is observed. The formation of 2-methyl benzimidazole was reported^[19] by early workers as a result of an intramolecular ring closure in the case of o-amino acetophenone. However, it was reacted selectively to yield the corresponding anilide under this condition.

Also ketoximes in the same conditions gave amides by Beckmann rearrangement. In a typical case, benzophenone oxime and P_2O_5/SiO_2 reagent were mixed together in an Erlenmeyer flask and placed in a domestic microwave oven and irradiated for 3 min. Benzanilide was obtained in 95% yield. The general reaction is illustrated according to the Sch. 2 and the results have been reported in Table 2. As shown in Table 2 corresponding amides was obtained in 75–95% yields.

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Table 1. One-pot preparation of amides from ketones by using P_2O_5/SiO_2 in solid phase under microwave irradiation.

Entr	y Substance	Tim (min	e 1) Products	Yields % of product ⁴ (isolated)	M.p./°C a found (lit.)
1		5	O NH	100 (88)	68–69 (68–70) ^[21]
2 3	PhCOPh PhCOCH ₃	5 8	PhCONHPh PhNHCOCH ₃ PhCONHCH ₃	100 (95) 85 (70) 15 75 (65)	$ \begin{array}{c} 164 \ (163)^{[20]} \\ 115 \ (115-6)^{[21]} \\ - \\ 101 \ 2 \ (105 \ 6)^{[20]} \end{array} $
5	PhCOCH ₂ CH ₃ PhCH ₂ COCH ₃	8 3	PhONHCOCH ₂ CH ₃ PhCONHCH ₂ CH ₃ PhCH ₂ NHCOCH ₃ PhCH ₂ CONHCH ₂	75 (65) 25 70 (63) 30	$\frac{101-3(103-6)^{1/3}}{58-59(61)^{[20]}}$
6	PhCH ₂ CH ₂ COCH ₃	3 3	PhCH ₂ CH ₂ CH ₂ NHCOCH ₃ PhCH ₂ CH ₂ CONHCH ₃	75 (68) 25	50-51 (51-52) ^[21]
7	Å	2	NH	98 (75)	231–3 (234–6) ^[22]
8	CH ₃	5	NHCOCH ₃	98 (95)	130–131 (132) ^[20]
9	PhCOCOPh	5	PhCONHCOPh	100 (85)	160-162 (163) ^[20]

^aIR, ¹H-NMR, and m.p. confirmed structures. Ratio of the isomers were determined from ¹H-NMR of the crude mixture.

In conclusion, this new method of nitrogen insertion reactions of ketones, without preliminarily oxime formation, offers significant improvements over the excising procedures and thus helps facile entry into a variety of amides or lactams.^[23] Also this simple and readily available reagent affords various amides in shorter reaction time, with excellent yields, and good selectivity without involvement of toxic and expensive material. Further studies of the new applications of P_2O_5/SiO_2 reagent in organic synthesis is in progress.

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Scheme 2.

Table 2. P₂O₅/SiO₂ mediated Beckmann rearrangement of oximes under microwave irradiation.

Entry	Substance	Products	Yields % of product ^a (isolated) ^b	M.p./ °C found (lit.)
1	NOH	O NH	100 (85)	68–69 (68–70) ^[21]
2	PhC(NOH)Ph	PhCONHPh	100 (95)	164 (163) ^[20]
3	PhC(NOH)CH ₃	PhNHCOCH ₃ PhCONHCH ₃	90 (80) 10	115 (115-6) ^[21]
4	PhCOC(NOH)Ph	PhCONHCOPh	98 (85)	160-162 (163)[20]
5	Кон	NH	98 (75)	231–3 (234–6) ^[22]

^aRatio of the isomers was determined from ¹H-NMR of the crude mixture.

^bYields refer to isolated pure compounds after column chromatography. IR, ¹H-NMR, and m.p. confirmed structures.

EXPERIMENTAL SECTION

All melting points recorded are uncorrected open capillary measurements. IR spectra were recorded on a Shimadzu-IR 470 spectrophotometer. ¹H-NMR spectra were recorded on a Bruker-80 and 500 MHz instrument using tetramethylsilane (TMS) as an internal standard. Silica gel 60 (230–400 mesh) was purchased from Fluka and was dried NĨ4

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in an oven at 120°C for 2 h. Irradiation was carried out in a domestic microwave oven (Electra, 2450 MHz, and 800 W) for optimized time.

Preparation of P_2O_5/SiO_2 reagent. A mixture of phosphorous pentoxide (6g) and chromatography grade silica gel (10g) were placed in a flask and stirred for 4h. This homogeneous, free flowing and white powder reagent is sensitive toward moisture and should be stored in a dessicator.

General procedure. In a typical reaction, a mixture of ketone (2 mmol), hydroxylamine hydrochloride (4 mmol) and reagent (1 g) were grounded thoroughly in a mortar. Usually an immediate color change was observed. The mortar was covered with a watch glass and put inside an Electra Microwave (2450 MHz, 800 W). The mixture was irradiated for the time indicated in Table 1. The completion of the reaction was monitored by TLC examination. After the completion of the reaction, the mortar was removed from the oven and the mixture was cooled at room temperature, and then 10 mL of 5% aqueous HCl was added to the mixture. The resulting solution was extracted with CH₂Cl₂ (2×10 mL). The extracts were combined and dried over CaCl₂. Evaporation of the solvent under vacuum gave amide with high purity (Entries 1, 2, 7–9) (based on TLC, ¹H-NMR, IR and melting point). Column chromatography or recrystallization from benzene or benzene-cyclohexane could further purify the products of Entries (3–6).

2-Amino acetanilide was obtained in 95% yield, m.p. 130–131°C Lit.^[20] (132°C). IR (KBr): $\nu = 3450$, 3320, 1640 cm⁻¹. ¹H-NMR (CDCl₃): δ 2.5 (s, 3H), 6.2 (b, 3H), 6.5–6.7 (m, 2H), 7.2 (t, 1H, J = 8 Hz), 7.7 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz).

α-**Camphidone** was obtained in 75% yield, m.p. 231–233°C Lit.^[22] (234–236°C). IR (KBr): $\nu = 3200$, 1660 cm⁻¹. ¹H-NMR (CDCl₃): δ 0.94 (s, 3H), 1.03 (s, 3H), 1.08 (s, 3H), 1.58 (m, 1H), 1.76 (m, 1H), 1.89 (m, 1H), 2.05 (m, 2H), 2.97 (d, 1H, J = 9 Hz), 3.47 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 2$ Hz), 5.75 (b, 1H).

N-Benzoyl benzamide was obtained in 85% yield, m.p. 160–162°C Lit.^[20] (163°C). IR (KBr): $\nu = 3100$, 1680 cm⁻¹. ¹H-NMR (CDCl₃): δ 7.4–7.7 (m, 6H), 8.1 (dd, 4H, $J_1 = 8$ Hz, $J_2 = 2$ Hz), 11.25 (b, 1H).

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