Letter

A Facile Synthesis of N-Alkoxyacylimidovl Halides from α -Nitro Ketones and Alkyl Halides in the Presence of NaHSO₄/SiO₂

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Abstract A novel method was developed for the synthesis of N-alkoxyacylimidoyl halide by the reaction of α-nitro ketone and alkyl halides in the presence of NaHSO₄/SiO₂. Nitrile oxides that are generated from α nitro ketones by silica gel supported acid catalysts are the possible intermediate, which react with alkyl halides to form N-alkoxyacylimidoyl halides. Novel 17 N-alkoxyacylimidoyl halides were synthesized by this procedure.

Key words alkoxyacylimidoyl halide, nitrile oxide, solid acid, one pot, stereoselective

N-Alkoxyimidoyl halides (3') are very useful synthetic intermediate because they can be transformed into various functional groups¹ and heterocycles,² and they are also employed for the C–C bond formations.³ Generally 3' are synthesized by the halogenation of O-alkyl benzaldoximes by using N-halosuccinimide, in which O-alkyl benzaldoximes were prepared by the alkylation of benzaldehyde oxime^{1f,4} or by the reaction of benzaldehyde with O-alkyl hydroxylamine⁵ (Scheme 1, a, method A).⁶ N-Alkoxyimidoyl halides (3') are also synthesized by the reaction of hydroxamates using phosphorus pentachloride,⁷ or phosphorus tribromide/bromine,⁸ or triphenylphosphine/tetrahalomethane⁹ (Scheme 1, a, method B). Although several methods for the synthesis of *N*-alkoxyimidoyl halides have been reported, only one report describes the preparation of N-alkoxyacylimidoyl halide (3); 3 (X = Cl) was prepared from α -methoxyphenylacetonitrile in four steps (Scheme 1, b), namely. (1) amidoxime was prepared from the reaction of α -methoxyphenyl acetonitrile with hydroxylamine; (2)



alkylation of amidoxime was carried out in order to obtain O-methyl- α -methoxyphenyl acetamidoxime; (3) the latter was then converted into the hydroximoyl chloride by nitrosative deamination in the presence of chloride ion; (4) the final step was the transformation of the α -methoxy group into a ketone functional group by reaction of the hydroximoyl chloride with N-bromosuccinimide (NBS) in the presence of a small amount of concentrated hydrobromic acid.¹⁰

In this report, **3** was considered as a potential precursor for the preparation of heterocyclic compounds because it contains two functional groups that can react with nucleophiles at the same time. Applicability of this useful synthetic precursor, **3**, will be extended if more simple synthetic methods for **3** are developed.

Solid acid catalysts have many advantages such as easy handling, easy isolation of the products and separation of the catalysts. Recently, we have reported various organic transformations, such as alkylation of β -dicarbonyls¹¹ and aromatics,¹² cross-coupling of alcohols,¹³ Ritter reactions,¹⁴ C–C bond cleavage¹⁵ and construction of heterocycles,¹⁶ by using silica gel supported sodium hydrogensulfate (NaHSO₄/ SiO₂) as solid acid catalyst. We herein report, for the first time, a simple one-pot synthesis of **3** from α -nitro ketones and alkyl halides using NaHSO₄/SiO₂ (Scheme 2).

The reaction of α -nitroacetophenone (**1a**, 1 equiv) with tert-butyl bromide (2a, 6 equiv) was carried out in the presence of NaHSO₄/SiO₂ (1 equiv; Table 1). The desired product **3aa** was obtained in 86% yield in cyclohexane at 80 °C for eight hours (Table 1, entry 1). To optimize the reaction condition, several solvents were tested; namely, 1,2-dichloroethane, mono- and dichlorobenzenes and toluene. All solvents tested gave 3aa in moderate to good yield (Table 1,

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Method A

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В





| Entry | Acid | Amount | Solvent | Yield (%)ª |
|-------|--------------------------------------|--------|--------------------|-----------------|
| 1 | NaHSO ₄ /SiO ₂ | 1 mmol | cyclohexane | 86 |
| 2 | NaHSO ₄ /SiO ₂ | 1 mmol | 1,2-dichloroethane | 55 |
| 3 | NaHSO ₄ /SiO ₂ | 1 mmol | monochlorobenzene | 88 |
| 4 | NaHSO ₄ /SiO ₂ | 1 mmol | o-dichlorobenzene | 69 |
| 5 | NaHSO ₄ /SiO ₂ | 1 mmol | toluene | 87 |
| 6 | H_2SO_4 | 1 mmol | toluene | 30 |
| 7 | TsOH·H ₂ O | 1 mmol | toluene | 62 |
| 8 | PPA/SiO ₂ ^b | 0.1 g | toluene | 20 |
| 9 | SA/SiO ₂ ^c | 1 mmol | toluene | 49 |
| 10 | Amberlyst 15® | 0.2 g | toluene | 69 |
| 11 | NaHSO ₄ ·H ₂ O | 1 mmol | toluene | NR |
| 12 | SiO ₂ | 0.5 g | toluene | 20 ^d |
| 13 | $ZnCl_2/SiO_2$ | 1 mmol | toluene | 0 ^e |
| 14 | none | - | toluene | NR |

^a Yields were determined by GLC.

^b Silica gel supported polyphosphoric acid was employed.

^c Silica gel supported sulfamic acid was employed.

^d No reaction took place.

e Reaction time was 16 min.

6 and 7) and heterogeneous (Table 1, entries 8–10) conditions but the reaction using a grained NaHSO₄·H₂O (Table 1, entry 11) was not effective. Silica gel also catalyzed the reaction to afford **3aa** in 20% yield (Table 1, entry 12). However, when silica gel supported zinc chloride (ZnCl₂/SiO₂) was used, *tert*-butyl toluene was formed by a Friedel–Crafts reaction instead of the expected product (Table 1, entry 13). In the reactions of *tert*-butyl halides (Table 2), the use of





a) General method for the synthesis of N-alkoxyimidoyl halide

Method B



b) A method for the synthesis of *N*-alkoxyacylimidoyl halide



Scheme 1 The synthetic methods for *N*-alkoxyimidoyl halide



entries 2–5). Although a high yield was obtained with cyclohexane, it was not an ideal solvent because of the poor solubility of **1a** and **2a**.

Therefore, we have used toluene as the standard solvent. Several acids were also tested. Brønsted acids promoted this reaction under both homogeneous (Table 1, entries

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Scheme 4 Synthesis of **3** using various α -nitro ketones

tert-butyl chloride (2b) in place of 2a gave the corresponding 3ab in 7% yield along with 38% yield of 3-benzoyl-5,5dimethylisoxazoline (4) and 21% yield of 3,4-dibenzoyl-1,2,5-oxadiazole 2-oxide (5; Scheme 3, a). Compound 5 was formed by a dimerization of benzoylmethyl nitrile oxide (6),¹⁷ which was confirmed by a selective formation of 5 by carrying out the reaction in the absence of 2. In the reaction using *tert*-butyl iodide (2c), only a trace amount of **3ac** was formed, but many unidentified by-products were formed.

The low yield of **3ac** was rationalized by secondary reactions of labile **3ac** with a large excess of **2c**. Therefore, we carried out this reaction by using 1.2 equivalents of 2c against 1a and obtained 27% yield of 3ac along with >8% of 4 (Scheme 3, b). When 2-bromo-2-methylbutane (2d) was used, 3ad was formed in 67% yield. On the other hand, secondary and primary alkyl bromides, 3-bromopentane (2e) and *n*-bromopentane (**2f**), did not give the corresponding 3ae and 3af but 5 was formed in these reactions. When bromodiphenylmethane (2g) was used for the reaction, pdiphenylmethyl toluene was formed by a reaction with the solvent in place of the expected **3ag**. However when 1,2-dichloroethane was used in place of toluene to avoid the reaction with the solvent, 3ag was formed in 33% yield. The reactions using benzyl bromide (2h) were carried out in toluene or in 1,2-dichloroethane, but the expected 3ah or alkylated toluene was not detected. In this reaction, 5 was formed as a major product. The scope of the reaction was investigated using various α -nitroketones with **2a** (Scheme 4). 1-Aryl-2-nitroethanones and 2-nitro-1-(2-thienyl)ethanones were converted into the corresponding N-tert-butoxyacylimidoyl bromides in good yields (3ba-ia). Reactions using 1-alkyl-2-nitroethanones also gave the corresponding products but with lower yields than those of **1a-j**. In the reactions of **11** and **1m**, which have longer alkyl chains, longer reaction time was required for the complete consumption of the starting materials.

¹H NMR spectra showed that all products consisted of a single stereoisomer in regard to the C=N double bond. X-ray crystal structure analyses of **3ag**. **3fa** and **3ia** revealed that the products were Z-isomers (Figure 1). Scheme 5 shows a plausible reaction pathway for the reaction of 1a with 2a.



Scheme 5 Proposed reaction pathway for the synthesis of 3

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^a Isolated yield.

^b The product was not detected.

^c 1,2-Dichloroethane was used as a solvent.

First, nitrile oxide (6) is formed from **1a** by dehydration with acid. In the absence of **2a** or in the presence of less reactive primary or secondary alkyl bromides, 6 is easily dimerized to 5. On the other hand, in the presence of 2a, the Z-isomer of **3aa** is formed. The formation of **6** is supported by our previous report; that is a synthesis of isoxazoles from **1a** and alkynes occurred in the presence of an acid, in which 6 was generated in situ and trapped an alkyne in order to obtain isoxazoles.¹⁸ Until today, 6 were mainly studied on 1,3-dipolar addition with unsaturated compounds, such as olefins, acetylenes, carbonyl compounds, and Schiff bases.¹⁹ As for the reactions of **6** with nucleophiles, some reactions with hydrogen halides,17 amines,20 acid anhydride²⁰ and thiols²¹ have been reported. However, to the best of our knowledge, our present report is the first example of the reaction of 6 with alkyl halides. The detailed pathway for the formation of the Z-isomer is now under investigation.

In conclusion, we have developed a simple one-pot synthesis of *N*-alkoxyacylimidoyl halides (**3**) from α -nitro ketones and alkyl halides in the presence of NaHSO₄/SiO₂ for



the first time.²² Seventeen novel compounds were easily synthesized by this procedure in good yields, and the products had Z-stereochemistry in regard to the C=N double bond. Further investigations about a detailed reaction pathway and application for heterocycle synthesis are now in progress.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588914.

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- (22) **Typical Procedure for the Synthesis of N-Alkoxyacylimidoyl Halide**: A mixture of α -nitro ketone **1** (1 mmol), alkyl halide **2** (6 mmol) and NaHSO₄/SiO₂ (2.1 mmol/g, 0.5 g) in toluene (10 mL) was stirred at 80 °C for 8 h, and then the used supported reagent was removed by filtration. The filtrate was evaporated to leave the crude product, which was purified by column chromatography (hexane–EtOAc) to obtain *N*-alkoxyacylimidoyl halide **3** (see Supporting Information).
 - **Typical Data for Representative Compound;** *N***-Diphenyl-methyloxy(benzoylformimidoyl Bromide)** (**3ag**): white solid; mp 71–72 °C (*n*-hexane). ¹H NMR (400 MHz, CDCl₃): δ = 7.62– 7.64 (m, 2 H), 7.49–7.53 (m, 1 H), 7.34–7.42 (m, 10 H), 7.24– 7.28 (m, 2 H), 6.46 (s, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 183.6, 139.6, 134.2, 133.5, 131.1, 130.9, 128.6, 128.3, 128.1, 127.5, 89.2. IR (neat): 1665, 1559 cm⁻¹. HRMS (ESI, MeOH): *m/z* [M + Na] calcd for C₂₁H₁₆NO₂NaBr: 416.0262; found: 416.0264. Anal. Calcd for C₂₁H₁₆NO₂Br: C, 63.97; H, 4.09; N, 3.55. Found: C, 64.06; H, 3.95; N, 3.53.