Tetrahedron Letters,Vol.24,No.31,pp 3255-3258,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

A NEW SYNTHESIS OF IMIDOYL IODIDES VIA BECKMANN REARRANGEMENT OF OXIME SULFONATES

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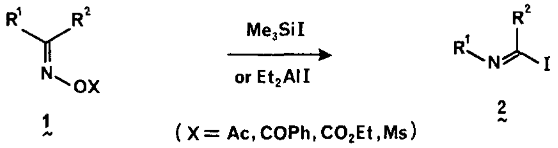
Summary: A new synthetic method of imidoyl iodides has been devised which involves the Beckmann rearrangement of oxime derivatives with trimethylsilyl iodide or diethylaluminum iodide. This allows a one-pot procedure for α-arylation of amines in synthetically useful yields.

Imidoyl iodide 2 is a highly intriguing class of activated amides in view of the ready susceptivility toward nucleophilic attack.[1] The synthetic utility of this reactive species, however, has been quite limited owing to the absence of the suitable preparative approaches and isolation procedures. Disclosed herein is a new and highly efficient method for the generation of imidoyl iodide 2 by treatment of oxime derivative 1 with trimethylsilyl iodide or diethylaluminum iodide. The reaction proceeds under mild conditions in aprotic media, thus allowing further transformation in situ with various nucleophiles.



When acetophenone oxime carbonate 3 in $CDCl_3$ in the NMR tube was treated with trimethylsilyl iodide (1.1 equiv) at 30°C for 10 min, the NMR spectrum clearly indicated the formation of the corresponding imidoyl iodide 4 (~100%).[2] Some examples of the reaction using other oxime substrates are listed in Table I. Reaction of 4, thus generated, with lithium ethanethiolate (2 equiv) in THF[3] gave

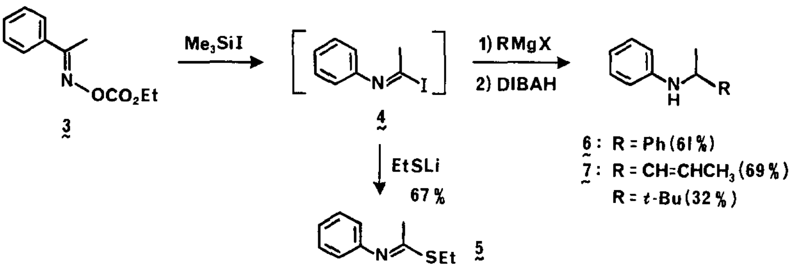
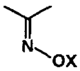
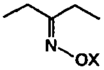
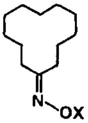
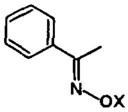
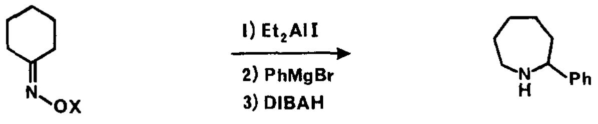


Table I. Synthesis of Imidoyl Iodides

oxime derivative	X	time (min)	temp (°C)	yield (%)[a]
	Ms	90	30	95
	COOEt	100	30	97
	COMe	90	30	54
	COPh	15	30	37
	Ms	10	0	96
	COOEt	45	30	85
	COOEt	10	30	100
	COMe	10	30	100

a) Yields were determined by integration of the pertinent peaks in the NMR spectra.

rise to the imino thioether 5 in 67% yield. Furthermore, a new carbon-carbon bond formation is readily achievable by using the appropriate Grignard reagents.[4] For example, direct treatment of 4 with phenyl- and 1-propenylmagnesium bromide (3 equiv) followed by reduction with excess DIBAH (4 equiv) produced the amines 6 (61%) and 7 (69%), respectively. In a similar manner, cyclododecanone oxime mesylate was transformed to α-phenylated amine in 51% yield. It should be noted that these amines cannot be synthesized by the previously reported Beckmann rearrangement-alkylation sequence using less reactive sp^2-carbon nucleophiles.[5] The whole process, however, has a lack of reproducibility except with acetophenone and cyclododecanone oxime derivatives. This drawback of the silicon method prompted us to explore another iodination agent and diethylaluminum iodide[6] was quickly found to be highly promising. Thus, reaction of cyclohexanone oxime mesylate 8 with diethylaluminum iodide (2 equiv) produced cleanly the imidoyl iodide, which was directly alkylated by the use of phenylmagnesium bromide (3 equiv) and then reduced with DIBAH (4 equiv) to furnish α-phenylated amine 9 in 81% yield. Other oxime

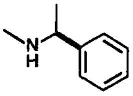


8

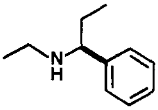
9 : X = Ms (81 %)
= CO_2Et (17 %)
= Ac (0 %)

derivatives such as cyclohexanone oxime carbonate and acetate gave less satisfactory results (0~17%).

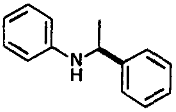
The effectiveness of this method is apparent from the following list of α-phenylated amines prepared from ketoxime mesylates by the aluminum method. Yields are indicated in parenthesis for each product.[7] A darkened bond appearing in a formula reflects the carbon-carbon bond created in the reaction of imidoyl iodides with Grignard reagents.



(92%)



(63%)



(44%)

The method for the conversion of oxime substrates to imidoyl iodides disclosed above makes available α-phenylated amines which are not accessible by previously described reactions.[5] This fact coupled with the efficiency of the present transformations should contribute to the facile synthesis of alkaloids possessing α-arylamino moiety such as nuphenine,[8] anabasine,[9] and papaverrubine A.[10]

The following experimental procedures for the aluminum as well as the silicon methods are illustrative.

N-(1-Phenylethyl)aniline (6). To a solution of oxime carbonate **3** (207 mg, 1 mmol) in dry CH_2Cl_2 (10 mL) was added trimethylsilyl iodide (157 μL, 1.1 mmol) at 0°C under argon atmosphere. After the mixture was stirred at 15°C for 1 h and cooled to -20°C, an ethereal solution of phenylmagnesium bromide (3 mL of a 1 M solution, 3 mmol) was added at -20°C. Then the mixture was stirred at this temperature for 1.5 h, poured onto sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, concentrated to ~10 mL, and treated with DIBAH (4 mL of a 1 M hexane solution, 4 mmol) at 20°C for 1 h. The reaction was terminated by dilution with CH_2Cl_2 (20 mL) followed by sequential treatment with NaF (672 mg, 16 mmol) and H_2O (0.22 mL, 12 mmol) at 0°C. The suspension thus obtained was vigorously stirred at 20°C for 30 min. Filtration by the aid of CH_2Cl_2 and removal of solvent left a liquid, which was purified by column chromatography on silica gel (ether/hexane, 1:5) to furnish **6** (120 mg, 61% yield) as a colorless oil.

2-Phenylazacycloheptane (9). To a solution of oxime mesylate **8** (191 mg, 1 mmol) in dry CH_2Cl_2 (10 mL) was added diethylaluminum iodide (2 mL of a 1 M hexane solution, 2 mmol) at -78°C. The resulting mixture was stirred at -78°C for 1 h and treated with an ethereal solution of phenylmagnesium bromide (3 mL of a 1 M solution, 3 mmol) at -78°C for 5 min and at 0°C for 1 h. Then DIBAH (4 mL of a 1 M hexane solution, 3 mmol) was added at 0°C. The whole mixture was stirred at 15°C for 1 h, poured onto a 10% NaOH solution, and subjected to extractive work up with CH_2Cl_2. Chromatography of the crude product on a silica gel column (i-$PrNH_2$/ether, 1:30) gave **9** (142 mg, 81% yield) as a colorless oil.

Acknowledgment. This work was generously supported in part by the Ministry of Education, the Japanese Government (Grant-in-aid, No. 118006) and the Toyo Stauffer Chemical Co., Ltd.

REFERENCES AND NOTES

1. For the chemistry of imidoyl iodides, see: Bonnett, R. "The Chemistry of the Carbon-Nitrogen Double Bond"; Patai, S., Ed., Interscience: New York, 1970; Chapter 13, pp 597-662; Ulrich, H. "The Chemistry of Imidoyl Halide", Plenum, New York, 1968.
2. **3**: ^{1}H NMR ($CDCl_3$) δ7.17-7.80 (5H, m, aryl CH), 2.36 (3H, s, CH_3); **4**: ^{1}H NMR ($CDCl_3$) δ6.58-7.50 (5H, m, aryl CH), 2.90 (3H, s, CH_3).
3. The lithium ethanethiolate was prepared *in situ* by treatment of the corresponding thiol with *n*-butyllithium at 0°C for 10 min.
4. Reaction of the stable imidoyl chloride, PhClC=NPh, with Grignard reagents was previously reported. See, Busch, M.; Fleischmann, M. *Ber*. **1910**, *43*, 2553; Busch, M.; Falco, F. *Ibid*. **1910**, *43*, 2557.
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6. We thank Toyo Stauffer Chemical Co., Ltd., for generous gift samples of aluminum reagents.
7. Yields were not optimized since these reactions were performed only once. Longer reaction time and higher reaction temperature might increase the yields of the reaction.
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(Received in Japan 23 April 1983)