



Indium triflate: a mild and efficient Lewis acid catalyst for O–H insertion reactions of α -diazo ketones

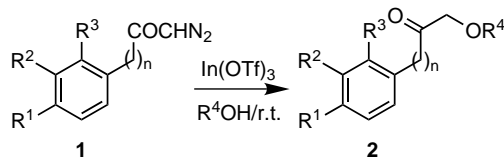
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Abstract—Facile O–H insertion reactions of α -diazo ketones with aliphatic/aromatic alcohols or benzenethiol have been developed in the presence of indium triflate as a catalyst. These reactions provided good yields of α -alkoxy ketones. A comparative study with other Lewis acids establishes the reactivity of indium triflate in O–H insertion reactions of α -diazo ketones. © 2002 Elsevier Science Ltd. All rights reserved.

The inter- and intramolecular formation of ether linkages through O–H insertion reactions of α -diazo ketones with aliphatic/aromatic alcohols catalyzed by copper or rhodium complexes has been well documented.¹ These reactions can also be carried out using protic acids² and strong Lewis acids.^{1a,3} For this purpose, the frequently encountered acid catalysts are dilute H₂SO₄ and AlCl₃ or BF₃·Et₂O, respectively. Copper or its chelate-catalyzed insertion reactions of diazo ketones with alcohols produces α -alkoxy ketones in competition with the formation of esters via the Wolff rearrangement.⁴ Recently, we reported⁵ our study on the decomposition of various α -diazo ketones to afford α -hydroxy ketones, bicycloalkane-1,3-diones and 3-furanones in the presence of Amberlyst-15.[®] Many of the above insertion processes suffered limitations such as the use of expensive catalysts, moderate product yields, competitive or slow reactions and the need for skillful work-up. Consequently, there is a need and scope for an improved procedure involving mild reaction conditions.



Scheme 1.

Keywords: alkoxy ketones; diazo ketones; indium triflate; Lewis acid catalyst; O–H insertion.

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Lewis acid-catalyzed reactions furnish versatile and selective routes to many natural/unnatural products in synthetic organic chemistry since this path rules out the use of corrosive Brønsted acid catalysts.^{6,7} Often traditional strong Lewis acids such as AlCl₃,^{7a} BF₃·Et₂O,⁸ TiCl₄⁹ and SnCl₄¹⁰ are employed as catalysts in organic synthesis. Although their role is well exploited in organic reactions, the use of Lewis acids such as the indium halides and indium triflate have been exploited as catalysts only in recent years.^{6d,e} The use of water tolerant Lewis acids has attracted some attention in recent years. In particular, the chemistry of metal triflates¹¹ has gained considerable attention as they provide selectivity and good yields of products.

It is evident from the literature¹² that indium triflate is a mild Lewis acid and it has received considerable attention in recent years as a catalyst. To the best of our knowledge, indium triflate has not been used in the decomposition of α -diazo ketones. As a part of our ongoing synthetic program¹³ on the reactions of α -diazo ketones, we herein report O–H insertion reactions of α -diazo ketones with aliphatic/aromatic alcohols or benzenethiol using In(OTf)₃ as the catalyst.

To a neat solution of diazoacetophenone in dry 1-butanol was added 10 mol% of indium triflate and the decomposition started with a slow evolution of nitrogen gas. The reaction mixture was stirred at room temperature under a nitrogen atmosphere and was followed by TLC until the disappearance of the starting material. In fact, diazoacetophenone was decomposed within 2 min, but the reaction was stirred for a further 3 min. The reaction mixture was then concentrated under reduced pressure and the crude reaction mixture was purified

Table 1. In(OTf)₃-catalyzed synthesis of α -alkoxy ketones

Product 2	R ¹	R ²	R ³	R ⁴	n	Time (min)	Yield ^a (%)
a	H	H	H	Bu	0	2	93
b	H	H	H	Pr	0	2	92
c	H	H	H	Et	0	2	90
d	H	H	H	Me	0	2	90
e	H	H	H	^t Pr	0	4	92
f	H	H	H	^t Bu	0	3	93
g	H	H	H	^t Bu	0	180	60
h	Me	H	H	Me	0	8	89
i	OMe	H	H	Bu	0	10	90
j	OMe	H	H	Pr	0	10	87
k	H	H	H	Pr	1	3	87
l	H	H	H	^t Pr	1	5	89
m	H	-CH=CH-CH=CH-		Et	1	3	83

^a Refers to yields (unoptimized) of isolated products **2**.

using neutral alumina column chromatography to furnish the α -alkoxy ketone **2a** in 93% yield (Scheme 1).

This reaction encouraged us to study further the decomposition of a variety of α -diazo ketones with indium triflate. We studied this reaction with various aromatic/aliphatic diazo compounds, all of which afforded the respective α -alkoxy ketones **2b–m** (Table 1) as a result of O–H insertion. It may be pointed out that all the reactions proceeded smoothly and in the case of both primary and secondary alcohols, they were completed in a short time to afford good yields of products, but the tertiary alcohol needed 3 h to proceed to completion. α -Diazo ketones involved in this work were prepared^{14a} according to literature precedent.^{1a}

It was interesting to investigate the indium triflate-catalyzed O–H insertion reaction using an allyl alcohol. Thus, we carried out the reaction of diazoacetophenone and geraniol in the presence of indium triflate (10 mol%) using dry benzene as the solvent. The reaction was stirred at room temperature for 0.5 h and purification of the crude reaction mixture afforded the ether **3a**^{14b} in 74% yield (Scheme 2) as the sole product. Similarly, the reaction of diazo-4-methoxyacetophenone with geraniol furnished product **3b** in 71% yield.

Further, we were eager to carry out O–H insertion reactions of α -diazo ketones with phenols using indium triflate. To a solution of diazoacetophenone and phenol was added 10 mol% of indium triflate at room temperature and the decomposition started with slow evolution of nitrogen gas. The reaction mixture was concentrated under reduced pressure and the crude reaction mixture was purified using neutral alumina column chromatography to furnish the α -alkoxy ketone **4a** in 51% yield (Scheme 3). Subsequently, we performed a similar experiment with 1- or 2-naphthol to afford products **4b** and **4c**^{14b} in 48 and 45% yields, respectively. It may be noted that Lewis acid catalysts often fail to afford insertion products with phenols as a result of the non-availability of the Lewis acid in the reaction mixture due to complex formation with the phenol.¹⁵

We decided to carry out a comparative study of O–H insertion reactions of an α -diazo ketone with an alcohol using other strong Lewis acids. To this end, we carried out the reaction of diazoacetophenone in neat dry 1-butanol using various Lewis acids under similar experimental conditions to afford product **2a**. The results are summarized in Table 2.

In a different experiment the O–H insertion reaction of diazoacetophenone with 1-propanol or 1-butanol using ytterbium triflate (12 mol%) afforded the corresponding insertion product in 3 h. Similarly, we performed the O–H insertion of diazoacetophenone with 2-propanol to afford 69% of product **2e** in 20 h. It may be noted that these reactions took longer reaction times.

Encouraged by the above results, we were also interested to carry out S–H insertion reactions of α -diazo ketones. We carried out the reaction of diazoacetophenone with benzenethiol in the presence of 10 mol% of In(OTf)₃ at room temperature for 15 min. Purification of the crude reaction mixture through a neutral alu-

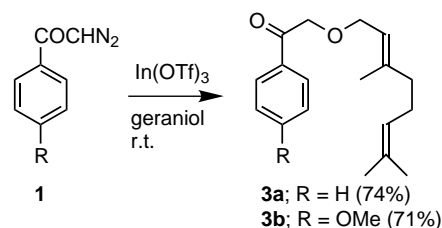
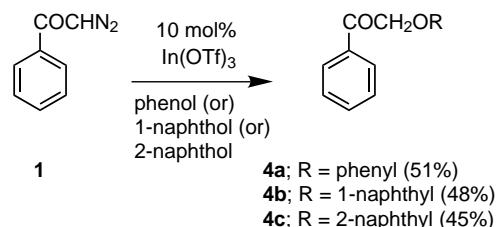
**Scheme 2.****Scheme 3.**

Table 2. O–H Insertion reaction of diazoacetophenone to 1-butanol using various Lewis acids

Lewis acids	Product 2a	
	Time (h)/mol%	Yield ^a (%)
ZnBr ₂	36/50	10 ^b
	50/100	45 ^b
Yb(OTf) ₃	5/5	55 ^b
	3/12	79
FeCl ₃	0.5/10	67 ^c
InCl ₃	12/10	– ^d
TiCl ₄	0.5/1.5	69
AlCl ₃	0.5/5	71 ^c
SnCl ₄	0.5/5	76
BF ₃ ·OEt ₂	0.5/5	74

^a Refers to yields (unoptimized) based on isolated product.

^b Refers to yields based on recovery of starting diazo ketone.

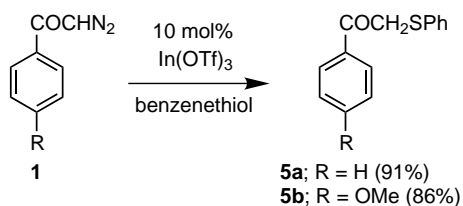
^c Reaction was quenched with brine solution instantly after disappearance of the diazo ketone.

^d Reaction did not occur even after 12 h.

mina column afforded product **5a** in 91% yield (Scheme 4). Similarly, the reaction of 4-methoxy diazoacetophenone with benzenethiol was performed under similar conditions to afford product **5b**.

The above results indicated that indium triflate provided good catalytic activity in the insertion reactions of α -diazo ketones with aliphatic/aromatic alcohols or benzenethiol. Use of smaller amounts of catalyst (<10 mol%) also furnished the respective products but with longer reaction times. Moreover, we have not observed any products arising from Wolff rearrangement.⁴ Recently, other methods involving the reactions of alkene with primary alcohols in the presence of CAN to furnish α -alkoxy ketones in moderate yield have also been reported.¹⁶ It is noteworthy that various natural products such as (\pm)-azaascorbic acid,¹⁷ chorismic acid and its phosphate analogues¹⁸ have been ingeniously approached via the O–H insertion reactions of α -diazo ketones with alcohols. Moreover, this methodology has been used for the synthesis of various important synthetic intermediates,^{1a} e.g. the O–H insertion reaction was applied to an enantiopure diol to form an adduct with ethyl diazoacetate suitable for elaboration into a chiral dimethyl 18-crown-6-ether.¹⁹

In conclusion, we have shown that the indium triflate-catalyzed insertion reactions of various α -diazo ketones with aliphatic/aromatic alcohols or benzenethiol provides the corresponding insertion products in a facile manner. This methodology is particularly attractive

**Scheme 4.**

since it will be an alternative to conventional insertion reaction processes.

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14. (a) **Typical experimental procedure for the preparation 2-diazo-1-phenylethanone**: A solution of benzoyl chloride (21 mmol) diluted with 40 mL of anhydrous ether was added dropwise to a solution of freshly prepared ethereal diazomethane (300 mL, 53 mmol) at 0°C over a 1 h period under an argon atmosphere. The resulting reaction mixture was stirred cold for an additional 0.5 h and then at room temperature for 1 h. After this period of time the excess diazomethane and ether were removed under reduced pressure using a liquid nitrogen trap in the hood. The resulting residue was subjected to a silica gel column (pre-washed using EtOAc) chromatography using 5% EtOAc–hexane eluent to afford 2-diazo-1-phenylethanone in 73% (2.25 g). The other diazo ketones involved in this work were prepared in a similar manner as described above from their corresponding acid chlorides; (b) **Typical experimental procedure for the insertion reactions using In(OTf)₃**: To a solution containing 2-diazo-1-phenylethanone (100 mg), geraniol (140 mg) in dry benzene (4 mL) was added indium triflate (10 mol%) and the mixture stirred at room temperature. Slow nitrogen evolution took place and the reaction mixture was followed by TLC until the disappearance of starting material. After 5 min the reaction mixture was concentrated under reduced pressure and purified by neutral alumina column chromatography (3% EtOAc–hexane) to afford product **3a** in 74% yield (138 mg). All new compounds gave satisfactory spectral data consistent with their structures. Selected spectral data, **2-(3,7-dimethylocta-2,6-dienyloxy)-1-phenylethanone (3a)**: colorless liquid, IR (neat) 2969, 2924, 2858, 1701, 1599, 1449, 1380, 1227, 1127, 911, 733 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.94 (d, 2H, *J*=7.6 Hz, Arom-H), 7.62–7.28 (m, 3H, Arom-H), 5.41 (t, 1H, *J*=7.0 Hz, =CH), 5.09 (t, 1H, *J*=7.0 Hz, =CH), 4.73 (s, 2H, OCH₂), 4.17 (d, 2H, *J*=7.0 Hz, OCH₂), 2.16–2.02 (m, 4H), 1.67 (s, 6H, CH₃), 1.60 (s, 3H, CH₃); ¹³C NMR (50.3 MHz, CDCl₃) δ 197.1 (C=O), 142.1 (*quat*-C), 135.5 (*quat*-C), 138.8 (=CH), 132.1 (*quat*-C), 129.1 (=CH), 128.3 (=CH), 124.3 (=CH), 120.4 (=CH), 72.8 (OCH₂), 68.1 (OCH₂), 40.0 (CH₂), 26.7 (CH₂), 26.1 (CH₃), 18.1 (CH₃), 16.9 (CH₃); mass *m/z*: 272 (M⁺). Anal. calcd for C₁₈H₂₄O₂: C, 79.37; H, 8.88. Found: C, 79.31; H, 8.82.
- 2-(Naphthalen-2-yloxy)-1-phenylethanone (4c)**: orange-red solid, mp 134–136°C; IR (KBr) 2362, 1705, 1631, 1600, 1469, 1215, 1178, 909, 737 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 8.05–8.01 (m, 2H, Arom-H), 7.79–7.67 (m, 3H, Arom-H), 7.62–7.23 (m, 6H, Arom-H), 7.12 (d, 1H, *J*=1.8 Hz, Arom-H), 5.37 (s, 2H, OCH₂); ¹³C NMR (50.3 MHz, CDCl₃) δ 194.8 (C=O), 153.3 (*quat*-C), 135.1 (*quat*-C), 134.7 (*quat*-C), 134.3 (=CH), 130.2 (=CH), 129.8 (*quat*-C), 129.3 (=CH), 128.6 (=CH), 128.1 (=CH), 127.3 (=CH), 126.9 (=CH), 124.5 (=CH), 119.1 (=CH), 107.8 (=CH), 71.3 (OCH₂); mass *m/z*: 262 (M⁺). Anal. calcd for C₁₈H₁₄O₂: C, 82.42; H, 5.38. Found: C, 82.34; H, 5.41.
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