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LETTERS

A novel indium-catalysed synthesis of tetra-substituted pyridine derivatives

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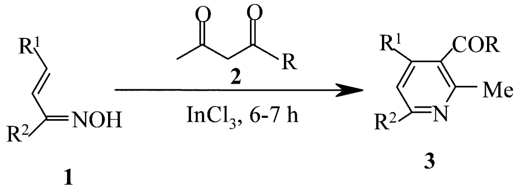
Abstract—Indium trichloride was found to be an effective catalyst for the synthesis of various tetra-substituted pyridine derivatives via Michael addition of β-dicarbonyl compounds to α,β-unsaturated oximes and subsequent ring closure.

Pyridine derivatives have attracted a great deal of interest, mainly concerning their synthesis, reactions and biological properties, as this structural motif appears in a large number of pharmaceutical agents and natural products.[1] They also find application as agrochemicals and anticancer agents.[2] Extensive studies have been carried out on the synthesis of these valuable compounds. The Vilsmeier–Hack reaction[3] of conjugated oximes is a multi-step process and involves a Beckmann rearrangement of the starting oximes. In the case of oximes derived from cyclic α,β-unsaturated ketones such a reaction is not possible. Recently amidrazone was reacted with unsymmetrical tricarbonyl compounds to provide a triazine, which subsequently reacted with norbornadiene to afford pyridine derivatives.[4] Bryce and co-workers have reported the synthesis of pyridine derivatives from furan precursors.[5] Also, gluteraldehyde can be cyclised to give pyridine in up to 53% yield by using an ammonium salt and malachite green or by copper(II) or iron(III) salts with halide counterions.[6] The reaction of methyl acetoacetate with *N*-benzylenimines in presence of LiI yielded pyridines[7] in 30–72% yield. In a very recent report,[8] an enamino ester and alkynone were reacted via Michael addition–cyclodehydration, catalysed by acetic acid/Lewis acid, but this Lewis acid-catalysed cyclodehydration is found to be more sluggish and less efficient than the corresponding reaction conducted in acetic acid. Therefore, the practical application of these methods suffer from several limitations. In view of current general interest in substituted pyridine derivatives,[9] there is a need for the development of a protocol using readily available and safe reagents, which leads to high yields of pyridine derivatives. We have developed a new one-pot reaction for the synthesis of tetra-substituted pyridine derivatives using $InCl_3$. The reaction proceeds efficiently in high yields, without the formation of any by-products.



$R = CH_3, OC_2H_5$
$R^1 = Ph$, *p*-*Cl*-C_6H_4, *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$
$R^2 = Ph, CH_3$

Scheme 1.

The emergence of indium(III) compounds as efficient Lewis acid catalysts, presents new and exciting opportunities for organoindium chemistry.[10] It was found that the low reactivity of trivalent organoindium reagents can be increased by complex formation with organolithium compounds.[11] The tetra-organo-indates thus prepared are sufficiently reactive to take part in reactions at ambient temperature.[11a] Moreover, indium metal[12] has been found to be an effective reducing agent and indium(III) halide complexes act[13a] as efficient, moisture compatible Lewis acid catalysts in Mukaiyama aldol reactions, Friedel–Crafts acylations,[12] Diels–Alder reactions[13b] in water and hetero Diels–Alder cycloadditions.[13c] However, its use in the Michael addition of β-dicarbonyl compounds to

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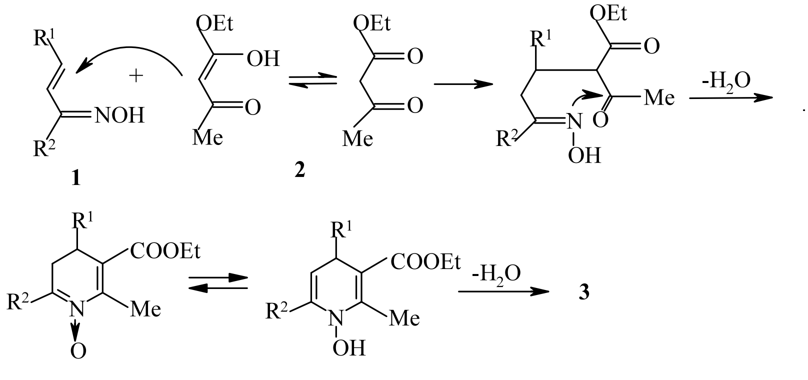
α,β-unsaturated oximes has remained unexplored.[14,15] In continuation of our studies on indium based reagents[16] we report herein the first example of indium trichloride mediated synthesis of tetra-substituted pyridine derivatives via Michael addition of β-dicarbonyl compounds to α,β-unsaturated oximes (Scheme 1).

Reaction of enone oxime **1a** with ethyl acetoacetate **2** (R = OEt) in the presence of indium trichloride without any solvent produced the corresponding tetra-substituted pyridine[17] **3a** as a pale yellow viscous oil in 80% yield. Analysis of the crude product did not indicate the formation of any other products. Similarly other substituted α,β-unsaturated oximes and β-dicarbonyl compounds were reacted together using indium trichloride following this procedure. The results are summarised in Table 1. This new method is fairly general and the reaction conditions are tolerant of the ether group. Aromatic halides showed selectivity to give the corresponding tetra-substituted pyridine derivatives without any products of dehalogenation or complex formation. However, the reaction was not as effective when acetyl acetone was used in lieu of ethyl acetoacetate and the corresponding tetra-substituted pyridine derivatives were obtained in only 50–60% yields (Table 1). It is worth mentioning that we have performed the Michael addition[18] of 1,3-dicarbonyl compounds with α,β-unsaturated ketones using bismuth trichloride and cadmium iodide under microwave irradiation. However, this reaction did not proceed with the enone oximes **1**. Attempts to perform the pyridine synthesis at ambient temperature for 24 h proved fruitless even when a large excess of $InCl_3$ was used. Further increase of the reaction time gave no significant improvement. Furthermore, the reaction did not proceed in the absence of indium trichloride and the reaction was ineffective when indium chloride was replaced with cerium chloride ($CeCl_3\cdot 7H_2O$), the corresponding tetra-substituted pyridine derivatives being obtained in poor yields of only 20–25%. In most cases, the reaction was complete within 6–7 h with indium trichloride, however, the reaction took longer with cerium chloride, approximately 10–12 h. Increasing the reaction time further gave no improvement in yields but instead decomposition of the starting materials occurred. All the compounds obtained were characterised fully by spectroscopic analysis (IR, ^{1}H NMR, and MS). Although the detailed mechanism of this reaction is not clear at this stage, it is likely that the reaction proceeds through the Michael addition of ethyl acetoacetate to the enone oxime followed by subsequent ring closure, dehydration and migration of a proton to form the *N*-hydroxy derivatives. Subsequent elimination of a further water molecule from this *N*-hydroxy derivative would provide the substituted pyridine. Further investigations of the scope and mechanism of the reaction are underway. A tentative mechanism for the formation of the tetra-substituted pyridine derivative is shown in Scheme 2.

Table 1. $InCl_3$-mediated synthesis of various tetra-substituted pyridine derivatives **3**

Product	R	R^1	R^2	Reaction time (h)	Yield[a] (%)
3a	OEt	Ph	CH_3	6	80
3b	OEt	Ph	Ph	7	80
3c	OEt	*p*-ClC_6H_4	CH_3	7	75
3d	OEt	*p*-$CH_3C_6H_4$	CH_3	6	80
3e	OEt	*p*-$CH_3OC_6H_4$	CH_3	7	75
3f	OEt	*p*-$CH_3C_6H_4$	Ph	7	80
3g	OEt	*p*-$CH_3OC_6H_4$	Ph	6	75
3h	CH_3	*p*-ClC_6H_4	Ph	8	60
3i	CH_3	*p*-$CH_3OC_6H_4$	Ph	8	60
3j	CH_3	*p*-$CH_3OC_6H_4$	CH_3	8	50
3k	CH_3	*p*-$CH_3C_6H_4$	CH_3	8	55

[a] All the yields refer to isolated chromatographically pure compounds.



Scheme 2.

In conclusion, we have provided a novel and efficient method for the synthesis of various tetra-substituted pyridine derivatives employing indium trichloride, which makes a useful and important addition to existing methodologies.[19] This new procedure has advantages such as the lack of side product formation and better yields than classical methods.

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17. In a typical case, ethyl acetoacetate (0.13 g, 1 mmol) and $InCl_3$ (0.22 g, 1 mmol) were added to enone oxime **1a** (0.16 g, 1 mmol) and the reaction mixture was heated with vigorous stirring to 150–160°C and kept at this temperature for 6–7 h (monitored by TLC). After that the unreacted ethyl acetoacetate (if any remains) was removed under reduced pressure. The residue was then taken in diethyl ether (25 mL) and the resulting mixture was extracted with 1 M HCl (3×20 mL). The combined acidic aqueous extracts were adjusted to pH 9 by means of aqueous ammonia and extracted with dichloromethane (2×20 mL). The dichloromethane extract was dried over anhydrous sodium sulphate and concentrated on a rotary evaporator to afford the crude tetra-substituted pyridine derivative **3a** in 82% yield which was then purified by column chromatography on silica gel using chloroform as eluent to give the pure ethyl 2,6-dimethyl-4-phenylpyridine-3-carboxylate **3a** as a light yellow viscous oil. **3a**: ^1H NMR ($CDCl_3$) δ 1.01 (t, $J=7.3$ Hz, 3H, OCH_2CH_3), 2.58 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.11 (q, $J=7.3$ Hz, 2H, OCH_2CH_3), 7.05 (s, 1H, pyridine-H_5), 7.25 (m, 5H, aromatics), IR (KBr): 2975, 2920, 1720, 1585, 1265, 1206, 1085, 870, 765, 700 cm^{-1}; δ_c 169.4, 159.2, 152.5, 150.9, 143.2, 130.46, 128.9, 127.9, 126.4, 121.6, 61.5 (CH_2), 24.3(Me), 23.2(Me), 14.0(Me); EI MS m/z 255. Calcd for $C_{16}H_{17}NO_2$: C,75.29; H, 6,67; N, 5.49. Found: C, 75.41; H, 6.74; N, 5.32. Similarly other enone oximes and β-dicarbonyl compounds were reacted in the presence of indium trichloride and the reaction times and yields are recorded in Table 1. All the compounds obtained were characterised fully by spectroscopic analysis (IR, ^1H NMR, MS) and finally by comparison with authentic samples.
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