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$InCl_3$-MEDIATED, SOLVENT FREE CONRAD-LIMPACH REACTION: FACILE AND EFFICIENT ONE POT METHOD FOR THE SYNTHESIS OF QUINOLONES

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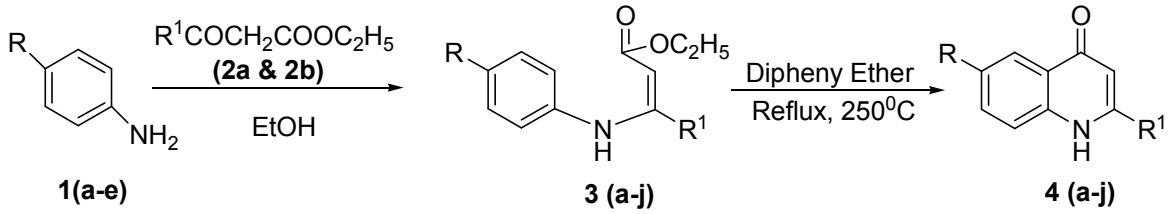
Abstract: A facile and efficient one pot method for the synthesis of 4-quinolones is described. 2-Alkyl and 2-aryl-4-quinolones **4 (a-j)** were synthesized in high yields employing Indium (III) chloride via Conrad-Limpach reaction of substituted amines **1 (a-e)** with β-ketoesters **2a & 2b** under solvent-free conditions at 100^0C without isolating the intermediary enamines **3 (a-j)**. The catalyst $InCl_3$ could be recovered and reused.

Key words: Conrad-Limpach cyclization, $InCl_3$, β-ketoesters , Quinolones.

Introduction:

Quinoline derivatives constitute an important class of N-heterocyclic compounds, many of which are found to occur naturally such as those in alkaloids and synthetic biologically active molecules[I]. 4-Quinolones[II] are also versatile synthetic intermediates due to their facile derivatization of the 4-hydroxyl group[III]. Many synthetic methods for 4-quinolones have been reported in literature[IV]. One classical and commonly used approach is the condensation of an arylamine **1** with β-ketoesters **2** in a suitable solvent under heating (80-100^0C) to afford the corresponding enamines (β-anilinoacrylates) **(3)**. The latter are then cyclized in high-boiling solvents such as diphenyl ether at high temperatures[V] (250° C) or under microwave[VI] (300° C) conditions to yield the quinolones **4**. This method suffers from the disadvantage that it is a two-step process requiring isolation of the preliminary condensation product **3** (involving loss of yield) and its subsequent cyclisation to **4** under high temperature conditions using a high-boiling solvent like diphenyl ether at 230-250^0C which is beset with twin problems of requiring solvent recovery & non-green conditions of reaction. (Scheme-I).

Scheme-I



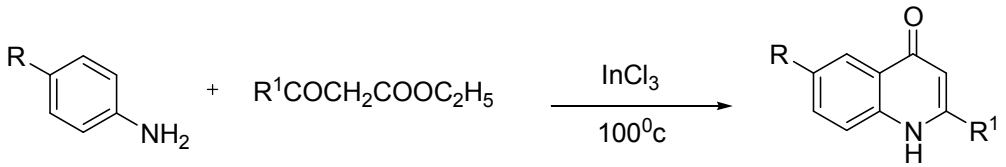
1(a-e) **3 (a-j)** **4 (a-j)**

Indium halides have been the subject of current interest because of their potential as Lewis acid catalysts in various organic transformations[VII]. In continuation of our research interest in the synthesis of quinolones[VIII, IX] herein we report a simple and efficient method for the synthesis of quinolones using catalytic amounts of Indium (III) chloride under solvent-free conditions.

Results and Discussions:

Arylamines **1 (a-j)** and β-ketoesters **2a & 2b** were reacted in the presence of $InCl_3$ without solvent at 100^0C for 30-40 mins to furnish 2-alkyl and 2-aryl-4-quinolones **4 (a-j)** in a manner similar to Conrad – Limpach synthesis in one go as clean products after simple processing.

Scheme-II



1 (a-e) **(2a & 2b)** **4 (a-j)**

The catalyst efficacy is fairly high; an increased reaction time resulted in no significant improvement. It is worth mentioning that the present procedure showed no evidence for the formation of side products. Various anilines and two β-ketoesters (ethyl acetoacetate, ethyl benzoyloacetate) were successfully employed (Table-I).

Table: I Reaction of **1(a-e)** with **2a & 2b** to obtain **4 (a-j)** in the presence of $InCl_3$ as Catalyst

Substrate	**Reagent**	**Product obtd.**	**Reaction Time (min)**	**Yield (%)**	**M.P (Lit M.P)^{o}C**
1a (R=H)	**2a**	**4a** (R =H, $R^1 = CH_3$)	40	87	234-236 (234)[X]
1b (R=OCH_3)	**2a**	**4b** (R = OCH_3, R^1=CH_3)	40	92	202-204 (201-202)[XI]
1c (R=Cl)	**2a**	**4c** (R =Cl, $R^1 = CH_3$)	50	88	>230 (>300)[XI]

1d (R=F)	**2a**	**4d** (R =F, $R^1 = CH_3$)	45	89	>230
1e ($R=CH_3$)	**2a**	**4e** (R =CH_3, $R^1 = CH_3$)	50	87	>230 (280)[XII]
1a (R=H)	**2b**	**4f** (R =H, $R^1 = C_6H_5$)	45	88	>230 (252-254)[XIII]
1b ($R=OCH_3$)	**2b**	**4g** (R =OCH_3, $R^1 = C_6H_5$)	40	89	>230 (302-304)[XIII]
1c (R=Cl)	**2b**	**4h** (R =Cl, $R^1 = C_6H_5$)	50	85	>230 (344-346)[XIII]
1d (R=F)	**2b**	**4i** (R =F, $R^1 = C_6H_5$)	48	86	>230 (294-296)[XIII]
1e ($R=CH_3$)	**2b**	**4j** (R = CH_3, $R^1 = C_6H_5$)	55	85	>230 (290-292)[XIII]

The reaction between aniline and β-ketoesters **2** such as ethyl acetoacetate **2a** & ethyl benzoyloacetate **2b** has also been attempted without adding any catalyst (neat conditions) which could be expected to be the most economical method. But, unfortunately, the reaction did not occur.

Different reagents, such as silica-sulphuric acid (SSA)[XIV], trifluoroacetic acid (TFA), $Sc(OTf)_3$, and p-TsOH were tried to study the reaction conditions between aniline **1** and ethyl acetoacetate

2a . From these results (Table-II), it is obvious that $InCl_3$ is the most adaptable and simplest catalyst for the synthesis of 2-alkyl and 2-aryl-4-quinolones.

In conclusion, this solvent-free procedure using a safe catalyst under mild reaction conditions provides an efficient, economical, and environmentally benign method for the synthesis of 2-alkyl and 2-aryl-4-quinolones.

Table:II Comparative study of various catalysts with aniline **1a** and ethyl acetoacetate **2a** for the synthesis of quinolones **4a**:

Catalyst used	**Time (min) of reaction**	**Yield*(%) of 4a**
None	50	No reaction
SSA	50	15
TFA	50	20
$Sc(OTf)_3$	50	30
p-TsOH	50	15
$InCl_3$	**40**	**87**

*Refers to isolated products

EXPERIMENTAL SECTION:

General Information:

Melting points were determined in open capillary tubes and are uncorrected. The progress of the reaction was monitored by Thin-layer chromatography (TLC) performed on silica gel G coated Merck plastic sheets and spots were observed by exposure to iodine vapour or UV light. IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer. ^1H NMR spectra were recorded on Brucker DPX-400 at 400-MHz (chemical shifts in δ, ppm). The spectra of our compounds were virtually identical with the published spectra.

Preparation of target molecules (General Procedure): A mixture of **1** (10 mmol) and **2a** (10 mmol) was heated at 100 °C in the presence of $InCl_3$ (10 mg) for a specified period of time (Table I) . The reaction was monitored by TLC. After completion of reaction, the crude residue was dissolved in 10 ml cold methanol and filtered to recover the catalyst as insoluble solid which was dried & reused. The methanolic filtrate containing the product was concentrated, then the residual crude products were recrystallized from suitable solvent to afford colorless crystals of target compounds **4**.

Characterization data:

6-fluoro-2-methylquinolin-4 (1H)one (4d): reaction time 45 min, yield 89 % ,m.p. >230 ^oC (R =F, $R^1 = CH_3$): IR (KBr): 1730 cm^{-1} (sharp, -C=O group); ^1H- NMR (400MHz, DMSO-d6/TMS): δ 2.32 (s, 3H, C_2-CH_3), 5.98 (s, 1H, C_3-H), 7.40-8.21 (m, 3H, Ar-H), 11.65 (s, 1H, NH). High Resolution mass: 178.0672 . Anal. Calcd for $C_{10}H_9NOF$ Requires C, 67.03; H, 5.62; N, 7.82; found C, 67.05; H, 5.65; N, 7.89 .

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