Re-Used Pph_3 Induced Chemoselective C-C Bond Formation for Synthesis of Novel Indolyl Quinoline Derivatives and their Alkylation Studies by TBAB

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Abstract

PPh_3 have been utilized as a novel and efficient chemoselective C-C bond formation, without alter active chlorine atom. This catalyst using for synthesis of novel Indolyl Quinolines by Knoevenagel condensation. The reaction of 2-chloroquinoline-3-aldehyde (2) with the active methylene compound, i.e. 3-cyanoacetylindoles (3), in ethanol at room temperature for 20 min to afford (E)-3-(2-chloroquinolin-4-yl-)-2-(1H-indole-3-carbonyl)acrylonitrile (4). Subsequently, these were reacted with benzenesulfonyl chloride in $CHCl_3$ the presence of tetrabutylammoniumbromide (TBAB) as an efficient phase transfer catalyst (PTC) to afford the corresponding derivatives i.e. (E)-3-(2-chloroquinolin-4-yl-)-2-(1-benzenesulfonyl-1H-indole-3-carbonyl)acrylonitrile (5). Compound 2 was prepared from acetanilide (1) using a well-known procedure by Vilsmeier-Hack reaction.
KEYWORDS – C-C bond formation, PPh_3, Knoevenagel reaction, TBAB phase transfer catalyst

I. INTRODUCTION

Knoevenagel condensation is an important carbon-carbon bond-forming reaction in organic synthesis [1]. Ever since its discovery, the Knoevenagel reaction has been widely used in organic synthesis to prepare coumarins and their derivatives, which are known to be important intermediates in the synthesis of cosmetics, perfumes and pharmaceuticals.[2] In recent times, there has been a growing interest in Knoevenagel products because many of them have significant biological activity [2]. The Knoevenagel reaction is generally carried out in the presence of weak bases such as ethylenediamine, piperidine and potassium fluroiodide etc [3-5]. In contrast, there are only a few acid catalysts that are known to promote this reaction [6]. Recently many efforts have been made to prepare olefinic compounds via the Knoevenagel reaction under heterogeneous conditions employing aluminum chloride, Xonotlite/tert- butoxide, cation-exchanged zeolites, alkali containing MCM-41, SiO_2, calcite or fluorite and NP/KF as heterogeneous catalysts [7-10] More recently, ionic liquids have also been employed to accomplish this reaction [11]. Earlier PPh_3 has been used in different reactions like preparation of 3-acetylindoles and 3-bis-indolylmethane derivatives [12], Diels–Alder synthesis of azabicyclo [2.2.2] octan-5-ones [13], mono- and bis-intramolecular imino Diels–Alder reactions for synthesis of tetrahydrochromano-quinolines [14] and Diels-Alder synthesis of pyranoquinoline, furoquninoline, and phenanthridine derivatives [15]. Chalcones having an α, β-unsaturated carbonyl group are one of the important biocides and versatile synthons for various chemical transformations [16] Most of the chalcones are highly biologically active with a number of pharmacological and medicinal applications [17] Chalcones have been used as anti HIV agents [18], cytotoxic agents with antiangiogenic activity [19], antimalarialsm [20].
Keeping in view the advantages of chalcones, we have carried out the synthesis of new Indoloylquinoline chalcones as potentially biologically active compounds by condensing

chemoselectively substituted 3-cyanoacetylindoles with 2-chloroquinoline-3-aldehyde in the presence of catalytic amount of PPh_3 in EtOH at room temperature only.

II EXPERIMENT AND RESULT

Treatment of each of the 3-cyanoacetylindoles **3(a-e),** independently, with 2-chloroquinoline-3-aldehyde **(2)** in the presence of PPh_3 in ethanol at room temperature, for 40-60 min, resulted in the formation of novel 3-(1H-indol-3-yl)-2-(2-chloro-quinolidene)-3-oxopropanenitriles **4(a-e)** respectively in 80-85% yields (Table 1 and Scheme 1). 2-chloroquinoline-3-carboxaldehyde (**2**) was prepared from, the commercially available, acetanilide (**1**) by treatment with the Vilsmeier-Hack reagent [23] using a known procedure. The progress of the reaction was monitored by TLC analysis of the reaction mixture for the disappearance of **1(a-e)** and **2** using hexane and ethyl acetate (7:3) as elluent.

All the compounds have been confirmed based on spectral and analytical data. Thus its IR spectrum in KBr showed absorption at 3300-3200 cm-1 (broad, medium, -NH of indole ring system), ≈ 2224 cm^{-1} (sharp, strong, –CN stretching) and ≈ 1665 cm^{-1} (strong, sharp, -CO stretching). For details please see Experimental Section.

This method is very facile and convenient for the preparation of large amount of Knoevenagel adducts with high yields in less time. PPh_3 acts as a mild Lewis base to induce the reaction. In the absence of PPh_3, the reaction does not proceed even after refluxing the reactants in ethanol for ≈ 24 h. The use of PPh_3 as a catalyst helps to avoid the use of environmentally unfavorable organic solvents (DMF, C_6H_6, DMSO, $CHCl_3$, MeCN etc.) as reaction medium.

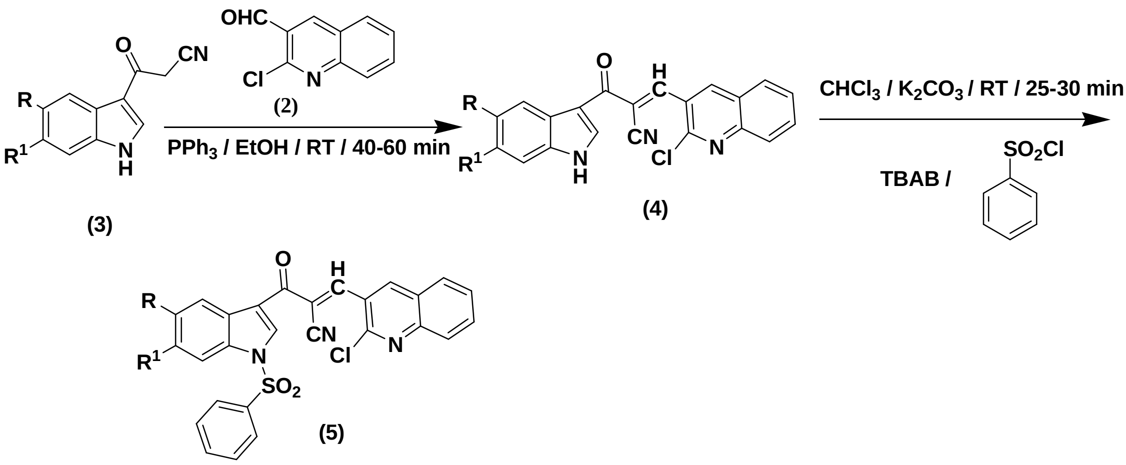

Figure 1. Synthesis of **4** from **3** & **2** in the presence of PPh_3

The above reaction was attempted using various bases like alc. NaOH, KOH, K_2CO_3 etc. in these reactions, the 2-chloroquinoline-3-aldehyde **(2)** was converted into 2-ethoxy-3-carboxaldehyde,[24] but in the presence of PPh_3 in EtOH medium yielded the end product **4** without the formation of any undesired product. Furthermore, the PPh_3 seems to be specific reagent for condensation of **2** with 3-cynaoacetylindole **(3)**. The PPh_3 it can be advantageously employed as base in these reactions, such as in the present case, where use of conventional bases like KOH, NaOH, NaOEt, or piperidine can trigger side reactions with an aldehyde reagent like 2-chloroquinoline-3-aldehyde.

The reaction of **4(a-e)** with benzenesulfonyl chloride in the presence of a weak base K_2CO_3 and catalytic amount of tetrabutylammonium bromide (TBAB) as phase transfer catalyst (PTC) in a suitable solvent at room temperature for 25-30 min gave **5(a-e)** in high yields (Scheme-1 and Table-1).

Chloroform seems to be the best choice among the solvents used for benzenesulfonyaltion of -NH grouping of **4**. The benzenesulfonylation of **4a→5a** was in different solvents in the presence of PTC conditions compared in Table 2. All the compounds have been confirmed based on spectral and analytical data. Thus its IR spectrum in KBr the absorption in the region ≈ 3300-3400 cm-1 was typically absent for all compounds showing the disappearance of -NH group of indole ring system. For details please see Experimental Section.

The above PTC methodology was applied for various heterocyclic compounds, like 5-((1H-indol-3-yl)methylene)- 2,2-dimethyl-1,3-dioxane-4,6-dione **6(a-b),** (E)-ethyl 2-cyano-3-(1H-indol-3-yl)acrylate **8(a-b),** 2-((1H-indol-3- yl)methylene)malononitrile **10(a-b)** and 3-acetylcoumarineindole **12 (a-b)** were smoothly converted into corresponding N-sulfonoyl derivatives **7(a-b), 9(a-b)**, **11(a-b)** and **13(a-b)** respectively**.** Finally observed in this reaction better yields are obtained in all cases when the reaction carried out in the presence of $CHCl_3$ solvent only. The all heterocyclic compounds **6**, **8**, **10** and 13 were synthesized in our laboratory. In the absence of PTC catalyst the sulfonation reaction does not move even applying vigorous conditions like heating, grinding, microwave etc. thus; this reaction is going on efficiently only in presence of PTC catalyst **Scheme-2**.

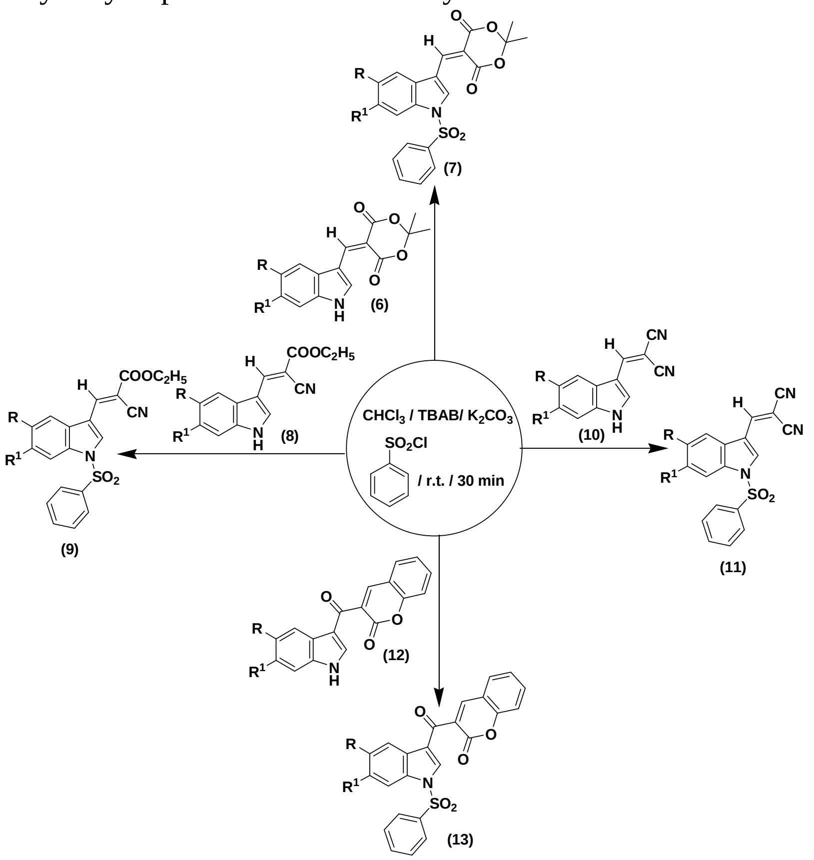

Figure 2. Preparation of various sulfonation derivatives of indoles

A plausible mechanism for the formation of **4** from **3** and **2** in the presence of PPh_3 as catalyst is shown in (Figure-3). First the PPh_3 abstracts the proton from 3-cyanoacetylindole **(3)** to form the carbanion of 3-cyanoacetylindole i.e. $\mathbf{3^{II}}$ which then attacks the protonated 2-chloroquinoline-3-aldehyde $\mathbf{(2^{I})}$ forming the corresponding intermediate $\mathbf{3^{III}}$ that loses water to form the end product **4,** Figure 3**.**

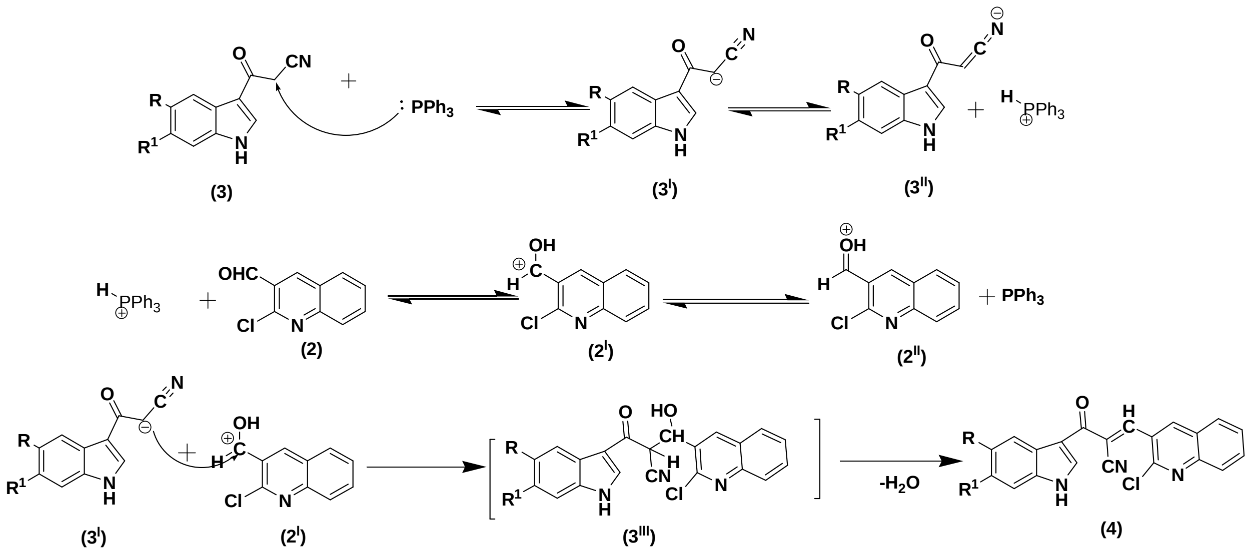

Figure 3: The plausible mechanism of formation of new series indolyl quinoline derivatives.

III.CONCLUSION

In summary, we have introduced efficient and specific catalyst i.e. triphenylphosphine (TPP) is using for the preparation of **4** in ethanol medium at room temperature only. This method is applicable to a wide range of 3-cyanoacetyllindoles, the attractive features of this procedure are the mild reaction conditions, high conversions, operational simplicity and readily available catalyst, all of which make it a useful and attractive strategy for the preparation of Knoevenagel adducts. Furthermore, TBAB is very effective phase transfer catalyst for making large amount of different heterocyclic substituted N-benzenesulfonyl derivatives.

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