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PhI(OAc)₂ mediated an efficient Knoevenagel reaction and their synthetic application for coumarin derivatives

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ABSTRACT

A phenyliododiacetate ($PhI(OAc)_2$) mediated an efficient and novel protocol for the Knoevenagel reaction has been successfully accomplished. A base free, simple and straightforward method afforded wide substrate scope and good functional group tolerance, having high yields (80-92%) under environmentally benign and mild reaction conditions.

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Introduction

The Knoevenagel condensation reaction is widely employed methods for the formation of C-C bonds¹ with numerous applications in the synthesis of fine chemicals,² hetero Diels-Alder reactions³ and in the synthesis of heterocyclic⁴ as well as carbocyclic compounds of various biological importance. Several active methylene compounds have been used as starting materials for the Knoevenagel condensation that include malononitrile, cyano-ethylacetate, ethyl-acetoacetate and arylidene-malononitriles, etc. In general, the Knoevenagel condensation is catalyzed by organic bases such as amines, pyridine, piperidine, a mixture of a secondary amine and amino acids such as L-proline. ⁵ The reaction also can be catalyzed by Lewis acids, including CdI₂,⁶ ZnCl₂,⁷ Al₂O₃,⁸ MgO, ZnO,⁹ TiCl₄,¹⁰ KF-Al₂O₃,¹¹ AlPO₄-Al₂O₃,¹² natural hydroxyapatite $(Ca_{10}(PO_4)_6(OH)_2)^{13}$ and ammonium acetate (NH₄OAc)-basic alumina.¹⁴ Because of the formation of undesirable side products the use of such bases/acids have led to environmental problems as to dispose large amount of organic wastes. For the reactions, electrochemical, microwave and ultrasound activation methods have also been reported.¹⁵ On the other hand, ionic liquids (ILs) are also well-known reaction media. In particular, "task-specific" ionic liquid catalysts with basic and acidic functional groups have been reported for the Knoevenagel reactions.¹⁶

Coumarins are class of oxygen containing heterocycles, found in numerous natural products including edible vegetables and fruits, with a benzopyrone skeletal framework.¹⁷ They are also used as additives in food and cosmetics, optical brightening agents and dispersed fluorescent, laser dyes and used as ligand in Suzuki miyaura and Mizorokie-Heck cross coupling reaction.¹⁸ They also displayed remarkable biological activity such as anti-HIV¹⁹, antifungal,²⁰ anti-inflammatory,²¹ anticancer,²² antimicrobial, antioxidant,²³ and dyslipidemic²⁴ activity. Derivatives obtained from 4-hydroxycoumarin protects liver cells from damage by peroxides.²⁵ Among these properties, cytotoxic effects were extensively studied.²⁶ Synthesis of coumarin derivatives can be achieved by Perkin, Pechmann, Wittig, Reformatsky, Claisen and Knoevenagel condensations.²⁷ The classical methods for the synthesis of 3-acetylcoumarin, ethyl coumarin-3-carbaoxylate and 3-cyanocoumarin is the Knoevenagel condensation using salicylaldehyde with ethyl acetoacetate, diethyl malonate and α -cyano-ethylacetate compounds respectively, followed by intramolecular cyclization (Scheme 1).²⁸ This traditional methods generally required harsh reaction conditions and often resulted in low product yields. Therefore, in organic synthesis an effective method for the straightforward synthesis of coumarins from simple, easily available and cheap starting materials is still in high demand. Reddy et. al. in 2013 described Cu-catalyzed A³ coupling reaction to afford coumarins using ethoxyacetylene, pyrrolidine and salicylaldehydes (Scheme 2).²⁹ In 2015, X. He et. al. reported the reaction of salicylaldehydes with Meldrum's acid in the presence of catalytic amount of anhydrous FeCl₃ in ethanol solvent for the synthesis of ethyl-coumarin-3-carboxylate (Scheme 3).³⁰ Recently, S. ⁵¹ In Fiorito et. al. successfully developed ytterbium triflate catalyzed and crop-derived products methods in the coumarins synthesis.³ the past few years, hypervalent iodine reagents, such as phenyliododiacetate (PIDA) have been used for the formation of C-C bonds, without involvement of a toxic, transition-metal-containing reagent.³² There are few examples reported for the oxidative C-C bond

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formation by hypervalent iodine reagent.³³ Herein, we report a facile methodology for Knoevenagel reaction and their application for coumarins synthesis using salicylaldehyde with α -substituted ethylacetate and PhI(OAc)₂ in ethanol.

Previous work:

Scheme 1.



Results and discussion

In an initial study, aldehyde **1** and cyano-ethylacetate **2a** were tested for the Knoevenagel reaction in the presence of PIDA, which afforded 90% and 92% yield of product respectively (Table 1, entry 3). To verify the role of PIDA, we performed a comparative experiment without PIDA. However, the reaction failed to afford the desired product **3a** and **4g** (Table 1, entry 1). It confirmed that PIDA is necessary to promote the process. To optimize the product yield, we also found that treating with 20 mol% (0.2 equiv.) of PIDA, generated trace amount of the desired product (Table 1, entry 2). When PIDA increased to 0.5 equiv., the product yield was enhanced (Table 1, entry 10). Use of 1.0 equiv. of PIDA afforded maximum yield (Table 1, entry 3). Fuerthermore, increase of PIDA 2.0 equiv., the product yield was decreased (Table 1, entry 9). The effects of molecular iodine and other hypervalent iodine reagents such as IBX, PhIO and Dess-Martin were investigated. In case of molecular iodine, no conversion was observed (Table 1, entry 5). Moreover, IBX, PhIO and Dess-Martin were catalyzed the process with lower yields and longer reaction time (Table 1, entries 6, 7 and 8). PIFA also gave the similar result (Table 1, entries 12-16). In addition, it was found that at high/refluxed temperature, no product formation was observed (Table 1, entry 11). Therefore, this reaction could be best performed with 1.0 equiv. PhI(OAc)₂ in ethanol at 35-40 °C for 0.5-1 h.





Entry

1

Reagent

(1 equiv.)

-

^aReaction condition: benzaldehyde/salicylaldehyde (1.0 mmol), cyano-ethylacetate (1.0 mmol) and PIDA (1.0 mmol) in ethanol (5 mL) at 35-40 °C. ^bPIDA (20 mol%). ^cPIDA (2.0 equiv). ^dPIDA (0.5 equiv). ^eat 80°C. ^fIsolated yields.



Reaction condition. Benzaldehyde (1.0 mmol, 0.1061gm), cyano-ethylacetate (1.0 mmol, 0.1131gm) and PIDA (1.0 mmol, 0.3221gm) in ethanol (5 ml) at 35-40 °C.

The substituent effects on the benzaldehyde ring were examined. Both electron-donating and electron withdrawing groups were well tolerated, and good to excellent yields of the corresponding substituted ethyl-2-cyano-3-phenylacrylate were obtained (Table 2). Replacing chloro in the **1a** to other halogen, such as bromo, did not affect the yield to any significant degree (**3d** and **3e**). We observed that, yield was slightly higher for electron withdrawing group (3c and 3h). Similarly, the para-substituted hydroxyl substrates with respect to aldehyde group slightly decreased the yield might be due to electron donating tendency via resonance (3f), which decreased the electrophilic nature of the aldehyde group.

Table 3. Synthesis of coumarin derivatives



Yield^f(%)

3a/4g

0/0

Time

(h)

1.0

Solvent

Ethanol

Tetrahedron

Reaction condition. salicylaldehyde (1.0 mmol, 0.1221gm), α -substuted ethylacetate (1.0 mmol) and PIDA (1.0 mmol, 0.3221gm) in ethanol (5 ml) at 35-40°C.

Salicylaldehyde **1a** bearing a variety of substituents on the benzene ring reacted very smoothly to afford the corresponding coumarins (**4a-r**) in 80-92% yield, indicated that the substituents on the aromatic ring of **1a** did not have significant influence on the reaction. Salicylaldehydes possessing several functional groups such as methoxy, hydroxyl, chloro, bromo and 2-hydroxy-1-naphthaldehyde were also tolerated in this reaction, and good yields of corresponding products were obtained. When ethyl-acetoacetate was subjected to the reaction, the corresponding product (**4a**) was obtained in 92% yield. Under the optimum conditions, cyano-ethylacetate and diethyl malonate were smoothly converted to 3-cyano-coumarin (**4g**) and ethyl coumarin 3-carboxylate (**4m**) in 92% and 90% yield, respectively (Table 3). However, some reactants required more reaction time. In addition, it was found that electron donating group at para position to aldehyde group converted slowly, the corresponding product (**4c**, **4i** and **4o**) was obtained in 82%, 80% and 84% yield respectively. While more conjugated system converted more smoothly and required less reaction time. The respective product (**4f**, **4l** and **4r**) was obtained in 91%, 91% and 92% yield respectively.

The structure elucidation of **3b** and **4b** was done on the basis of the collective information obtained from various spectroscopic techniques such as ¹H-NMR, ¹³C-NMR and GC-MS. Disappearance of aldehyde proton in ¹H NMR spectrum of **3b** and **4b** and appearance of singlet at δ 8.14 and δ 8.47 ppm respectively confirmed the formation of product **3b** and **4b**. In ¹³C-NMR spectrum of **3b** and **4b** showed eleven and twelve signals respectively. Further the structure of the product **3b** and **4b** was confirmed by HRMS. The m/z molecular ion peak of compound 3b and 4b appears as [M + Na]⁺ at 254.0746 and 242.0504.

In order to understand the reaction mechanism, we examined the reaction of salicylaldehyde **1a** with α -substituted ethylacetate **A** promoted by PhI(OAc)₂ **B** at room temperature. On the basis of literature report,³⁴ a possible reaction mechanism is proposed (Scheme 5). First, salicylaldehyde **1a** reacted with PhI(OAc)₂ **B** to form the reactive species **C**. Further, **C** reacted with α -substituted ethylacetate (enol form) **A** and converted into **E**. Then, adduct **E** converted into **F** by the elimination of PhIO, ethyl alcohol, acetic acid and intramolecular cyclisation.

Scheme 5. Proposed mechanism



Conclusion

In conclusion, we have developed a highly efficient and environmental friendly method for Knoevenagel reaction and their synthetic application for coumarin derivatives using $PhI(OAc)_2$ in good to excellent yield under mild reaction conditions. This method tolerated a wide range of functional groups.

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 General procedure: α-substituted ethylacetate (1.0 mmol) and Phenyliododiacetate (1.0 mmol) was dissolved in ethanol (5 ml) with constant stirring. After 10 minutes benzaldehyde /salicylaldehyde (1.0 mmol), was added and the mixture was allowed to stir for appropriate time. Then the progress of the reaction was monitored by thin layer chromatography. After completion of reaction as indicated by TLC, ethanol was evaporated under reduce pressure. The product was extracted with ethyl acetate, dried over Na₂SO₄ and solvent was evaporated under reduce pressure. The residue obtained was recrystallized by ethyl acetate and hexane to product 3a-3h and 4a-4r. Characterization data: Compound 3b, White solid; Yield: 86%; ¹H NMR (CDCl₃, 400 MHz) δ ppm 8.14 (s, 1H), 7.97 (d, J = 8.88 Hz, 2H), 6.97 (d, J = 8.88 Hz, 2H), 4.34 (q, J = 7.13, 2H), 3.87 (s, 1H), 1.36 (t, J = 7.12 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ ppm 163.86, 163.19, 154.45, 133.71, 124.45, 116.29, 114.84, 99.44, 62.49, 55.69, 14.23; Compound 4a, White solid; Yield: 92%; ¹H NMR (CDCl₃, 400 MHz) δ ppm 8.49 (s, 1H), 7.65-7.61 (m, 2H), 7.35 (d, J = 9.28 Hz, 1H), 7.31 $(d, J=7.56~Hz, 1H), 2.70~(s, 3H); {}^{13}C~NMR~(CDCl_3, 100~MHz)~\delta~ppm~195.54, 159.24, 155.28, 147.45, 134.39, 130.20, 124.96, 124.45, 118.21, 100~MHz)$ 116.63, 30.50; GC-MS (m/z): 188 [M+., C11H8O3].

Tetrahedron Highlight

- Highly efficient method for Knoevenagel reaction. •
- Excellent yield under mild reaction condition. •
- Less reaction time. •
- Accepter

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