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New catalyzed way to prepare chromeno[4,3-b]quinolin-6-ones

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ABSTRACT

A new and reliable protocol for the quantitative synthesis of chromeno[4,3-b]quinolin-6-ones has been developed by one-pot reaction of substituted anilines and 4-chloro-3-formylcoumarin using supported ionic liquid [pmim]HSO_{4SiO2}. The protocol offers the advantages of mild reaction conditions, short reaction times and high yields.

KEYWORDS

Coumarin;
Anilines;
Chromeno-quinoline.

INTRODUCTION

Functionalized quinoline derivatives are integral component of several natural products which are used as antibacterial,[1] antiasthmatic,[2] antifungal,[3] antiinflammatory[4] and anticancer[5] agents. Further, they are qualified as valuable starting materials for the synthesis of nano and mesostructures with improved electronic and photonic properties.[6] The synthesis of quinoline derivatives thus continues to be an active area of heterocyclic chemistry research, and the synthesis of various substituted quinolines has been largely explored.[7] On the other hand, coumarin derivatives are known to be equally important molecules endowed with wide spectrum of medicinal properties including antibacterial,[8] antiinflammatory,[9] antitumor[10] and anti-HIV[11] activities.

Chromeno-quinolines are fused poly heterocyclic systems comprising both coumarin and quinoline motifs which are known to possess interesting biological properties like bacteriostatic activity,[15] glucocorticoid modulators,[16] antiinflammatory effects[17]. Thus the structural features and the biological applications prompt intense research by the organic chemists for the development of novel methodologies for their synthesis.

RESULTS AND DISCUSSIONS

Chromeno[4,3-*b*]quinolin-6-one derivatives (1-8) are important class of chromeno-quinolines and the most conventional approach for their synthesis involves the reaction of 4-hydroxycoumarins with anilines and paraformaldehyde at 220–240æ%C under vacuum.[19] Tabakovic *et al.* have reported their synthesis starting from 4-hydroxycoumarin under Vilsmeier-Haack conditions.[20] Asherson *et al.* have reported their synthesis from 3-((dimethylamino)methyl)-4-hydroxy-2Hchromen-2-one and anilines but with lower yields.[21] Haber *et al.* have demonstrated stoichiometric $AlCl_3$ catalysed synthesis of the compounds by using 4-chloro-3-formylcoumarin and aniline in refluxing tetrahydrofuran.[22] All the above methods require either Lewis acid catalysts or high temperatures for their synthesis.

In view of the enormous potential of chromeno[4,3-

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b]quinolin-6-ones for various biological applications, we have envisaged an operationally benign ionic liquid catalyzed for their synthesis under mild conditions (scheme 1).

First, 4-chloro-3-formylcoumarin and aniline were reacted with fresh supported ionic liquid [pmim]HSO_{4SiO2} in various solvents. The fused chromeno-quinolines were obtained in different solvents with varying reaction rates and yields. The results show that choice of solvent has profound effect on both the rates of reaction and yields. While the reaction did not proceed in water, solvents like dichloromethane and chloroform gave comparatively lower yields. Acetonitrile afforded 76% while ethanol afforded 84% yield. Ethanol proved to be the solvent of choice which afforded 90% of the required product as a white precipitate in 6h.

The optimized reaction conditions were further extended to the reaction of various aniline substrates possessing diverse electronic features making the protocol rather general and the results are listed in TABLE 1. For example, the electron-rich anilines having *p*-Me, *p*-OMe functional groups afforded the respective products with yields between 90 and 92%. Similarly, the electron withdrawing *p*-nitroaniline afforded the required product in 94% yield.

A plausible mechanism for the synthesis is proposed in scheme 2. The first step of the reaction involves nucleophilic attack of aniline on 4-chloro-3-formylcoumarin. The intermediate formed by *N*-alkylation. The second step involves the activation of the aldehyde group by the *in situ* generated HCl as well as ionic liquid, promoting the cyclization of the aromatic ring to generate next intermediate. Elimination of the water molecule in the final step affords fused quinoline products 1-8.

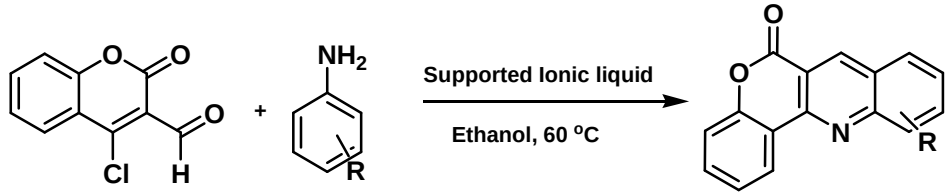
EXPERIMENTAL

Synthesis of chromeno[4,3-b]quinolin-6-one 1-8

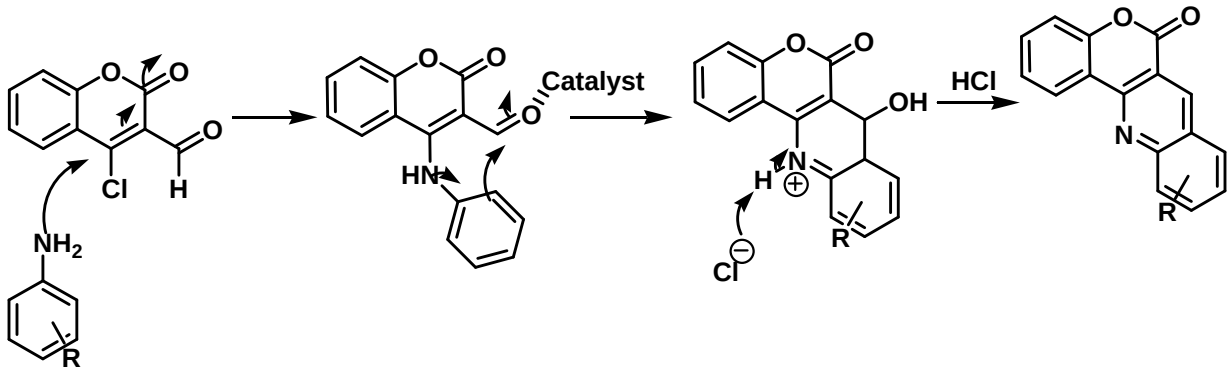
The supported ionic liquid catalyst has been prepared according to the literature.[23] A mixture of 4-Chloro-3-formylcoumarin (1 mmol) and aniline (1 mmol) in 5 ml of ethanol were reacted in the presence of the ionic liquid catalyst in 60 °C. The progress of the reactions were monitored by TLC (ethylacetate:*n*-hexane 1:3). Upon the completion of the reaction, the heterogeneous catalyst was separated from the mixture. After cooling, the resulting white precipitation was filtered and washed with Et_2O to yield 1-8 in high yields.

6H-Chromeno[4,3-b]quinolin-6-one (1)

White solid. 1H NMR (100 MHz, $CDCl_3$): δ 9.24 (s, 1H), 8.85 (m, 1H), 8.25 (d, 1H), 8.04 (m, 1H), 7.91 (m, 1H), 7.62 (m, 2H), 7.49 (m, 2H); ^{13}C NMR (CDCl3): 160.3, 158.4, 152.7, 146.7, 134.5, 132.4,



Scheme 1 : Synthesis of a series of chromeno-quinoline derivatives



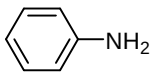
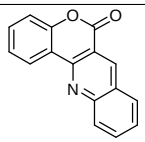
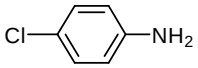
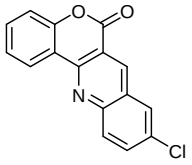
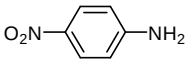
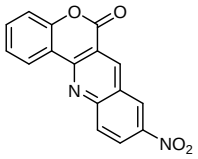
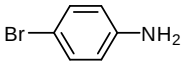
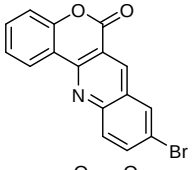
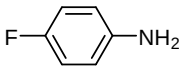
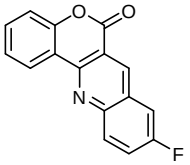
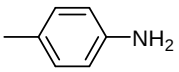
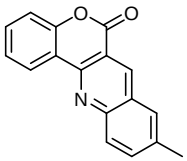
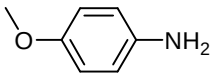
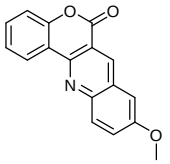
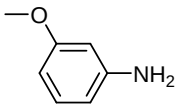
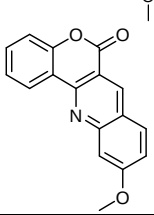
Scheme 2 : The proposed mechanism

128.6, 128.1, 127.0, 126.6, 124.2, 122.5, 119.6, 118.6, 118.7, 114.4; IR (KBr, *v*max/cm^{-1}): 1735, 1732, 2965; EI-MS: m/z = 247.06.

9-Chloro-6H-chromeno[4,3-b]quinolin-6-one (2)

White solid. ^{1}H NMR (100 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.77 (m, 1H), 8.19 (d, 1H), 8.01 (d, 1H), 7.86 (m, 1H), 7.61 (m, 1H), 7.44 (m, 1H), 7.26 (s, 1H); ^{13}C NMR ($CDCl_3$): 160.9, 152.8, 149.9, 149.5,

TABLE 1 : Synthesis of a series of chromeno[4,3-b]quinolinone

product	Aniline	Product	Time (h)	Yield (%)
1			7	90
2			8	88
3			8	90
4			9	86
5			7	88
6			6	92
7			7	90
8			6.5	91

139.9, 134.3, 133.4, 132.6, 131.2, 127.8, 127.7, 125.3, 125.1, 119.4, 117.5, 116.6; IR (KBr, *v*max/cm^{-1}): 3061, 1744, 1176

9-Nitro-6H-chromeno[4,3-b]quinolin-6-one (3)

Yellow solid. ^{1}H NMR (100 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.73 (m, 1H), 8.16 (d, 1H), 8.01 (d, 1H), 7.82 (m, 1H), 7.60 (m, 1H), 7.44 (m, 1H), 7.24 (s, 1H); 13C IR (KBr, *v*max/cm"^{1}): 1735, 1743, 1179; EI-MS: m/z = 292.25.

9-Bromo-6H-chromeno[4,3-b]quinolin-6-one (4)

White solid. ^{1}H NMR (100 MHz, $CDCl_3$): δ 9.20 (s, 1H), 8.76 (m, 1H), 8.45 (s, 1H), 7.89 (d, 1H), 7.73 (m, 1H), 7.63 (m, 1H), 7.45 (m, 1H), 7.26 (s, 1H); IR (KBr, *v*max/c^{-1}): 1737, 1734, 1174; EI-MS: m/z = 326.14

9-Methoxy-6H-chromeno[4,3-b]quinolin-6-one (7)

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.75 (m, 1H), 8.15 (d, 1H), 7.56 (m, 2H), 7.41 (m, 2H), 7.26 (s, 1H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$): 161.5, 158.4, 152.4, 147.7, 147.5, 138.8, 132.2, 131.7, 131.1, 128.5, 126.9, 124.8, 119.8, 117.3, 115.9, 105.6, 55.7; IR (KBr, *v*max/cm^{-1}): 2990, 1735, 1737, 1237; EI-MS: m/z = 277.07

10-Methoxy-6H-chromeno[4,3-b]quinolin-6-one (8)

White solid. ^{1}H NMR (100 MHz, $CDCl_3$): δ 9.20 (s, 1H), 8.86 (m, 1H), 7.39-7.62 (m, 5H), 7.26 (s, 1H), 3.99 (s, 3H); IR (KBr, *v*max/cm^{-1}): 3063,1734, 1735, 1181; EI-MS: m/z = 277.07.

CONCLUSION

In conclusion, we have reported an efficient, and new methodology for the synthesis of fused chromeno[4,3-b]quinolinone derivatives. The present methodology offers the advantages of mild reaction conditions, short reaction times; high yields and avoids the requirement of Lewis acid catalysts.

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