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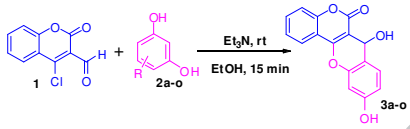

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ABSTRACT

Efficient and facile synthesis of 7H-benzopyrano[3,2-c]coumarins has been achieved by mild base promoted reaction of 4-chloro-3-formylcoumarin with diversely functionalized resorcinols. All the products were obtained as pure precipitates from the reaction mixture and the structure of the product was confirmed by X-ray analysis.

Resorcinol and their derivatives have been extensively used in organic chemistry for the synthesis of broad range of drug molecules with numerous biological implications.[1] They are admired as versatile starting materials for the development of photoelectronic materials and macrocyclic molecular scaffolds.[2] The positioning of the meta substituted phenols on the aromatic ring facilitate appropriate electronic features for a variety of tandem cylization protocols. These electronic features of resorcinols were exploited extensively for the synthesis of a variety of important structural scaffolds such as resorcinarenes, [3a] isofalvones, [3b, 3c] coumarins, [3d] chromenes[3e] and pyrans[3f].

Benzopyrano [3, 2-c] chromen-6-ones which are fused combination of privileged scaffolds such as coumarin and benzopyran constitute an elite class of structures. In addition to the individual applications of these scaffolds,[4] the fused motifs append significant contribution to the library of vital drug molecules with antifungal, insecticidal, anticancer, anti-HIV, anti-inflammatory, and antibacterial activities.[5] Due to the interesting conjugative properties of these structures, applications were established in the area of photonic materials.[6] The above remarkable biological and synthetic applications encouraged the development of some interesting procedures for the synthesis of these structures. For example, I. M. EI-Deen *et al*. reported the synthesis of benzopyrano[3, 2-c]chromen-6-ones using 3-ethoxycarbonylcoumarin and resorcinol in sodium methoxide conditions.[7] Kidwai *et al*. reported the laccase enzyme catalyzed synthesis of substituted benzopyrano[3, 2-c]chromen-6-ones by reaction of α,β-unsaturated coumarins with resorcinol, catechol and 1,4-hydroquinones in aqueous medium.[8] Wang *et al*. demonstrated a multicomponent reaction of 4-hydroxycoumarin, aldehydes and β-naphthol using $Zr(HSO_4)_4$ as catalyst successfully achieving the target benzopyrano [3,2-c]chromen-6-ones.[9] Ma *et al*. reported a modified experimental procedure of Wang *et al*. with melamine trisulfonic acid as catalyst under solvent-free conditions.[10] A. K. Bagdi *et al*. accomplished the synthesis of these compounds via copper(II) triflate catalyzed tandem reaction of 4-hydroxy coumarin with α,β-unsaturated carbonyl compounds.[11] However, most of the above reported procedures employ harsh reaction conditions to achieve the target molecules.

Recently, we have reported 4-chloro-3-formylcoumarin as a versatile starting material with unique structural features comprising a leaving group, α,β-unsaturated double bond and reactive aldehyde.[12d] Our latest endeavors demonstrated its application for the synthesis of novel heterocyclic scaffolds such as benzazepines, pyrymidine-N-oxides, quinolines, chromeno-2,6,9-trioxabicyclo[3.3.1]nonadienes and chromeno[4,3-b]pyridine-2,5-dione heterocyles.[12] To achieve the novel benzopyrano[3,2-c]coumarin target structures **3a-o**, we conceived a mild base promoted tandem protocol involving 4-chloro-3-formylcoumarin **1** and resorcinols **2a-o**, where the cyclized products can be obtained with intact alcohol moieties. We conducted a series of initial optimization experiments by subjecting 4-chloro-3-formylcoumarin **1** and resorcinol **2a** to various base catalyzed reaction conditions (Table 1).

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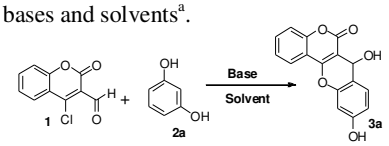
Table 1. Screening studies of the reaction of **1** and **2a** with various bases and solvents[a].

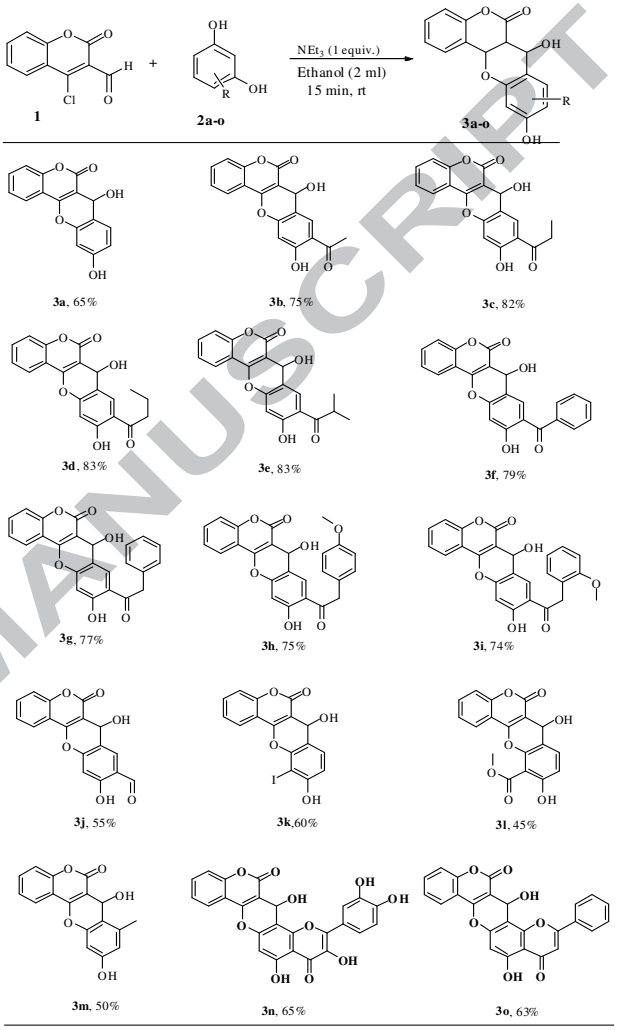


Entry	Base	Solvent	Time(min)	Yeild[c] (%)
1	NEt_3	EtOH	15	65[b]
2	K_2CO_3	Ethanol	60	NR[d]
3	NaOAc	Ethanol	60	NR
4	$NaHCO_3$	Ethanol	60	NR
5	DBU	Ethanol	15	60
6	DABCO	Ethanol	15	55
7	DIEA	Ethanol	15	60
8	-	Ethanol	60	-
9	NEt_3	$CHCl_3$	15	40
10	NEt_3	DCM	15	42
11	NEt_3	THF	15	55
12	NEt_3	Acetonitrile	15	55
13	NEt_3	Methanol	15	65

[a] Carried out with 1 mmol of **1** and 1 mmol of **2a** in the presence of with 1 equvivalent of base and solvent (3 mL) at at room temperature for 15min,
[b] pure precipitated yield,
[c] isolated yields,
[d] NR=no reaction.

Gratifying result was observed when **1** and **2a** were treated with 1 equivalent of triethylamine in ethanol, where the desired product **3a** was obtained directly as pure precipitate in 65% yield (Table 1, entry 1) within 15 minutes. Additionally, various bases such as K_2CO_3, NaOAc, $NaHCO_3$, DBU, DABCO and DIEA were investigated for the optimization studies. While inorganic bases such as K_2CO_3, NaOAc, and $NaHCO_3$ did not afford the product (Table 1, entries 2-4); organic bases DBU, DABCO and DIEA gave moderate yields (55-60%) of the desired product (Table 1, entries 5-7). Further, to ascertain the role of the base, a blank experiment was by conducted in the absence of base in ethanol which did not afford required product (Table 1, entry 8). Among various solvents screened (Table 1, entries 9-13), the reactions in $CHCl_3$, DCM, THF, CH_3CN, and MeOH gave poor to moderate yields of the product (40-65%). Although ethanol and methanol gave similar yields, ethanol was chosen for further experiments, as it facilitated direct precipitation of the product simplifying the protocol by avoiding the need for tedious column separations.

To explore the generality of the methodology, **1** was subjected to reaction with diversely functionalized resorcinol substrates under the above optimized experimental conditions (Scheme 1). Resorcinols possessing acyl substitutions such as acetyl, propanoyl, butanoyl, isobutyryl, benzoyl, phenacyl, p-methoxypheanacyl and o-methoxyphenacyl groups at the 4th position of the resorcinol ring (**2b-i**), afforded the corresponding products **3b-i** as pure precipitates from the reaction mixture in good to excellent yields (75-84%). When substrate **2j** with a formyl group in the 4th position of resorcinol was employed under the reaction conditions, product **3j** was obtained in moderate yield (55%)**,** due to the formation of other unidentified side products probably resulting from the reactive aldehyde group. When substrates **2k** and **2l** with functional groups positioned between the phenols were employed under the reaction conditions, moderate yields (45-60%) of their corresponding products **3k** and **3l** were obtained. Similarly, 5-methyl resorcinol **2m** under the reaction conditions afforded the product **3m** in moderate yield (50%). The lower yields in case of **2k-m** can be attributed to the steric factors which can hinder either *O*-alkylation or intramolecular cyclization steps of the reaction. The scope of the reaction was further investigated with readily available bulkier nutraceutical substrates containing resorcinol scaffolds such as quercetin dihydrate **2n**, and chrysin **2o**. Interestingly, despite multiple reactive phenolic groups on these substrates, both the substrates reacted selectively affording good yields (63-70%) of the corresponding products **3n** and **3o** as pure precipitates. In general, all the products were precipitated in pure form from the reaction mixture which simplified work-up and purification procedures.



Scheme 1: Synthesis of benzopyrano coumarins scaffolds[13]

During close monitoring of the reaction it was observed that the reaction was initiated instantaneously after the addition of the reactants where all the reactants were consumed within 15 minutes and prolonged reaction times did not improve the yields any further. Interestingly, we were successful in isolating *O*-alkylated resorcinol precipitates within 30 seconds of the initiation of the reaction exclusively for the resorcinols **2g-i** (see supplementary data), whereas other substrates reacted more rapidly to yield the products directly, making the isolation of *O*-alkylation intermediates difficult.

The structure of the product was confirmed by X-ray analysis of **3f** as shown in Figure 1. The molecule was crystallized in monoclinic system with space group $P2_1/c$ with four molecules in the unit cell. The crystal was stabilized by O-H...O hydrogen bonding interaction between two molecules resulting in a dimer in the unit cell (Also refer crystal data and crystal packing diagram in supplementary data).

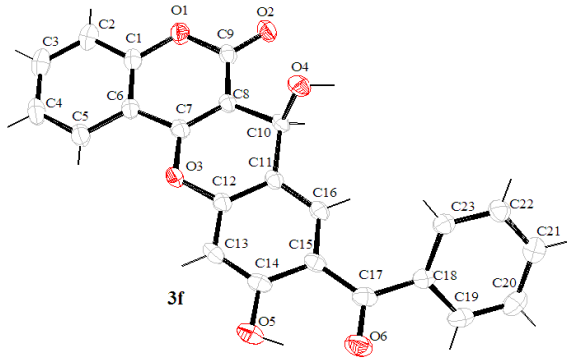
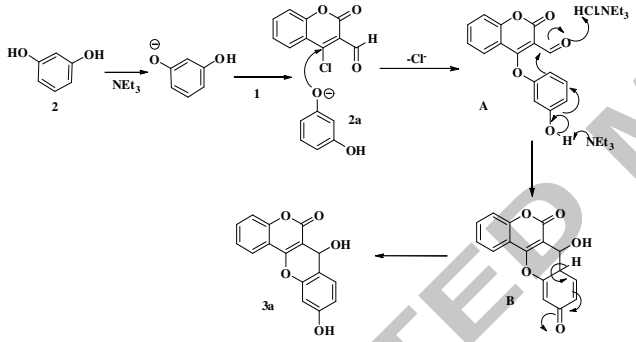


Fig. 1. ORTEP plot for the X-ray crystal structure of **3f** at 30% probability.

Based on the observations from Scheme 1, we envisaged the mechanism as shown in Scheme 2 to account the formation of the products **3a-o**. As shown in the Scheme 2, triethylamine initiates the reaction by abstracting the proton from resorcinol **2a** generating resorcinolate anion which participates in a nucleophilic substitution reaction at the 4-chloro position of **1** resulting in an *O*-alkylated intermediate **A.** Intermediate **A,** then undergoes intramolecular electrophilic aromatic substitution reaction with the formyl group of **1** affording the cyclized intermediate **B**, which rearranges to the yield the final product benzopyrano[3,2-c]coumarin-6-one **3a**.



Scheme 2. Mechanism for the formation of **3a**.

In conclusion, we have reported a mild and efficient synthesis of benzopyrano[3,2-c]coumarins via base promoted tandem nucleophilic addition and electrophilic aromatic cyclization reaction. The protocol afforded all the products as pure precipitates in good to excellent yields. Further studies on biological activities and photochromic applications are currently being explored.

Acknowledgments

We thank the administration of Sankar Foundation for their kind support.

Supplementary data

General experimental section, analytical data for compounds **3a-o** and the X-ray analysis of **3d** can be found in supplementary data. Crystallographic data of **3d** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 971586 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

References and notes

1. Durairaj**,** Raj B. Resorcinol: Chemistry, Technology and Applications; Springer: New York, **2005**.
2. Livingstone, R. A.; Thompson, J. O. F.; Iljina, M.; Donaldson, R. J.; Sussman, B. J.; Paterson, M. J.; Townsend, D. *J. Chem. Phys.* **2012,** *137*, 184304.
3. (a) Hoegberg, A. G. S. *J. Org. Chem.*, **1980**, *45*, 4498 ; (b) Singh, H.; Pratap, R. *Tetrahedron Lett.* **2006**, *47*, 8161; (c) Lang'at-Thoruwa, C.; Song , T, T.; Hu, J.; Simons, A. L.; Murphy, P. A. *J. Nat.Prod.* **2003**, *66*, 149; (d) Laufer, M. C.; Hausmann, H.; Hölderich, W. F. *Journal of Catalysis*. **2003**, *218*, 315; (e) Kale, S, R.; Kahandal, S. S.; Burange, A. S.; Gawande, M. B.; Jayaram, R. V. *Catal. Sci. Technol.* **2013**, *3*, 2050; (f) Radwan, S. M.; Bakhite, E. A.; El-Dean, A. M. K. *Phosphorus, Sulfur, and Silicon and the Related Elements*. **1995**, *101*, 207.
4. (a) Ellis, G. P.; Lockhart, I. M. the Chemistry of Heterocyclic Compounds: 31, 1196, New York, **2007**; (b) Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M.; Comprehensive Heterocyclic Chemistry II: 5, 301, Pergamon Press, Oxford, **1996**; (c) Geen, G. R.; Evans, J. M.; Vong, A. K.; Comprehensive Heterocyclic Chemistry II: 5, 469, Pergamon Press, Oxford ,UK, **1996**; (d) Rukachaisirikul, V.; Tadpetch, K.; Watthanaphanit, A.; Saengsanae, N.; Phongpaichit, S. *J. Nat. Prod*. **2005**, *68*, 1218; (e) Velozo, L. S. M.; Ferreira, M. J. P.; Santos, M. I. S.; Moreira, D. L.; Emerenciano, V. P.; Kaplan, M. A. C. *Phytochemistry*. **2006**, *67*, 492; (f) Chinese Meteria Medica, Jiangsu New Medical College, Ed.; Shanghai People's Pub. House, Shanghai, **1977**, 2506; (g) Iwata, N.; Wang, N.; Yao, X.; Kitanaka, S. *J. Nat. Prod.* **2004**, *67*, 1106; (h) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G. Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc*. **2000**, *122*, 9954; (i) Oh, S.; Jang, H. J.; Ko, S. K.; Ko, Y.; Park, S. B. *Journal of Combinatorial Chemistry*. **2010**, *12*, 4; (j) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G. Q. *J. Am. Chem. Soc*. **2000**, *122*, 9968; (k) Gong, Y. D.; Seo, J.; Chon, Y. S.; Hwang, J. Y.; Park, J. Y.; Yoo, S. *J. Comb. Chem.* **2003**, *5*, 577–589; (l) Hwang, J. Y.; Choi, H. S.; Seo, J.; La, H. J.; Kim, D. S.; Jeon, H. S.; Jeon, M. K.; Lee, D. H.; Gong, Y. D. *J. Org. Chem.* **2005**, *70*, 10151.
5. (a) Mali, R. S.; Joshi, P. P.; Sandhu, P. K.; Manekar-Tilve, A. *J. Chem. Soc. Perkin Trans.*1. **2002**, 371; (b) Page, P. C. B.; Appleby, L. F.; Day, D.; Chan, Y.; Buckley, B. R.; Allin, S. M.; McKenzie, M. J. *Org. Lett.* **2009**, *11*, 1991; (c) Shen, Y. C.; Wang, L. T.; Chen, C. Y. *Tetrahedron Lett.* **2004**, *45*, 187; (d) Fong, W. F.; Shen, X. L.; Globisch, C.; Wiese, M.; Chen, G. Y.; Zhu, G. Y.; Yu, Z. L.; Tse, A. K. W.; Hu, Y. J. *Bioorg. Med. Chem.* **2008**, *16*, 3694; (e) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K. H. *J. Med. Chem.* **2001**, *44*, 664; (f) Su, C. R.; Yeh, S. F.; Liu, C. M.; Damu, A. G.; Kuo, T. H.; Chiang, P. C.; Bastow, K. F.; Lee, K. H.; Wu, T. S. *Bioorg. Med. Chem.* **2009**, *17*, 6137; (g) Galinis, D. L.; Fuller, R. W.; McKee, T. C.; Cardellina II, J. H.; Gulakowski, R. J.; McMahon, J. B.; Boyd, M. R. *J. Med. Chem.* **1996**, *39*, 4507; (h) Nicolaides, D. N.; Gautam, D. R.; Litinas, K. E.; Hadjipavlou-Litina, D. J.; Fylaktakidou, K. C. *Eur. J. Med. Chem.* **2004**, *39*, 323; (i) Melliou, E.; Magiatis, P.; Mitaku, S.; Skaltsounis, A. L.; Chinou, E.; Chinou, I. *J. Nat. Prod.* **2005**, *68*, 78.
6. Huang, C. N.; Kuo, P. Y.; Lin, C. H.; Yang, D. Y. *Tetrahedron* **2007**, *63*, 10025.
7. EI-Deen, I. M.; Ibrahim, H. K. *Journal of the Korean Chemical Society*. **2003**, *47*, 137.
8. Kidwai, M.; Poddara, R.; Diwaniyan, S.; Kuhad, R. C. *Synthetic Communications*. **2011**, *41*, 695.
9. Wang, X.; Lu, G.; Yan, F.; Ma, W.; Wu, L. *J. Heterocyclic Chem.*, **2011**, *48*, 1379.
10. Ma, W.; Wang, X.; Yan, F.; Wu, L.; Wang, Y. *Monatsh Chem.* **2011**, *142*, 163.
11. Liu, Y.; Zhu, J.; Qian, J.; Jiang, B.; Xu, Z.; *J. Org. Chem.* **2011**, *76*, 9096.
12. (a) Prasad, J. V.; Prabhakar, M.; Manjulatha, K.; Rambabu. D.; Solomon, K, A.; Krishna, G. G.; Kumar, K. A. *Tetrahedron Lett.* **2010,** *51*, 3109; (b) Prasad, J. V.; Reddy, J. S.; Kumar, N. R.; Solomon, K. A.; Gopikrishna, G. *J. Chem. Sci.* **2011,** *123*, 673; (c) Jalli, V. P.; Jaggavarapu, S, R.; Kamalakaran, A. S.; Gangisetty, S. K.; Nanubolu, J. B.; Gopikrishna, G. *Tetrahedron*

Lett. **2013,** *54*, 1491; (d) Jaggavarapu, S. R.; Kamalakaran, A. S.; Gayatri, G.; Shukla, M.; Dorai, K.; Gopikrishna, G. *Tetrahedron*, **2013,** *69*, 2142.

13. **Representative experimental procedure for synthesis of compound 3a**: **Synthesis of 7, 10-dihydroxy-7H-benzo [5, 6]-pyrano [3, 2-c] chromen-6-one (3a)**: A solution of 4-chloro-3-formyl coumarin (1 mmol), resorcinol (1 mmol) and triethylamine (1 equivalent) in 5ml ethanol were stirred at room temperature for 15 min. After completion of the reaction the precipitate obtained was filtered and washed thoroughly with absolute ethanol and re-crystallized from ethanol to afford pure product **3a**. Brown colored solid, mp 153-154 °C; [Found: C, 68.08; H, 3.56; $C_{16}H_{10}O_5$ requires C, 68.09; H, 3.57;%]; ν_{max}(KBr) 1719, 1702, 1679, 1618, 1583, 1479, 1418, 1240, 1041 cm^{-1}; δ_H (400 MHz $CDCl_3$) 12.12 (1 H, s), 8.29 (1H, s), 8.18 (1 H, d, *J* 7.2 Hz), 7.79 (1H, t, J 7.2Hz),7.43-7.13 (4H, m),7.10 (1 H, d, *J* 6.8 Hz), 5.89 (1H, d, J6.8Hz); δ_C (100 MHz, $CDCl_3$) 187.76, 159.84, 159.20,, 152.57, 145.68, 138.61, 137.14, 133.53, 129.78, 129.64,127.02, 126.07,125.98, 125.13, 118.77, 114.50, 103.35, 31.41.; LCMS: MH^+, 332.