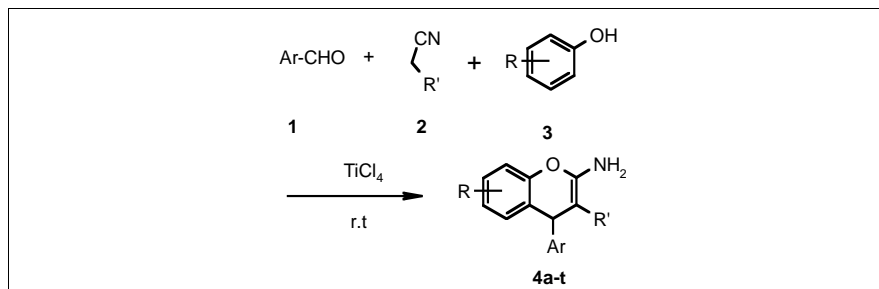


B. Sunil Kumar, N. Srinivasulu, R. H. Udupi, B. Rajitha\*, Y. Thirupathi Reddy, P. Narsimha Reddy and P. S. Kumar

Department of Chemistry National Institute of Technology, Warangal (AP), India

E-mail: [nr\\_penthala@yahoo.co.in](mailto:nr_penthala@yahoo.co.in)

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Three component coupling of one pot reaction which serves as the most convenient route to the synthesis of benzopyran derivatives using the TiCl<sub>4</sub> catalyst (10 mol %) under solvent free conditions is described. The procedure offers a systematic method with a number of advantages including operational simplicity, neat reactions, reduced reaction time, high yields of products and applicability to large scale reactions.

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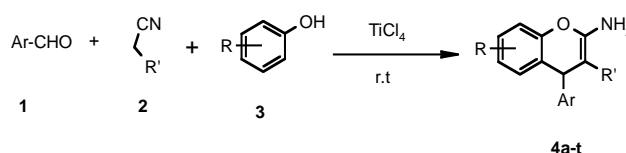
## Introduction.

Ideal synthesis is one in which the target component is produced in one step in quantitative yield from readily available and inexpensive starting material in source effective environmentally acceptable process [1]. Benzopyrans constitute structural units of several natural products [2] and are known to have diverse pharmacological activities [3-6] depending of the nature of substituents attached at a specific position. Members of this group display a broad range of applications as additives to food and cosmetics, pigments [7], fragrances, optical brightening agents, dispersed fluorescent and tunable dye lasers [8]. In recent years benzopyran derivatives have attracted strong interest due to their useful pharmacological properties such as anticoagulant, antianaphylactic, spasmolytic, diuretic, anti-bacterial, antifungal, insecticidal, anticancer [9], and potential biodegradable agrochemicals [10].

Many conventional synthetic methods, which are used to prepare benzopyran derivatives, involve three component one pot condensation of active methylene compounds with an aromatic aldehyde and activated phenol using base or amide as catalyst [11]. But some of these methods are plagued by the limitations of poor yield and difficult workup procedure. TiCl<sub>4</sub> has been reported as a good catalyst for a number of organic reactions such as reduction [12], esterification [13], hydroamination [14] and other synthetic reactions [15]. However there were no reports on synthesis of polyfunctionalized benzopyrans using TiCl<sub>4</sub>. Hence the alternative synthetic method of

these derivatives is of much interest. In this communication we wish to report a general highly efficient route for the synthesis of benzopyran derivatives using the inexpensive and commercially available catalyst TiCl<sub>4</sub> under solvent free conditions.

## Scheme I



The mixture of active methylene compound, an aromatic aldehyde and an activated phenol under solvent free conditions was stirred at room temperature for stipulated time in the presence of TiCl<sub>4</sub> until the reaction is completed. The resulting benzopyran was extracted with a suitable solvent, dried, concentrated and the product thus obtained was recrystallized from appropriate solvent.

It was observed that the nature of the substituents does not play a vital role in terms of yields under this reaction condition. All the aldehydes used for the reaction provided benzopyran derivatives in high yields, the presence of electron donating or electron withdrawing group on the aromatic ring of aldehydes, irrespective of their positions in the ring did not make any obvious difference in terms of yields of the benzopyran

Table 1  
Synthesis of Benzopyrans from Naphthols, Alkyl Cyanoacetates and Aromatic Aldehydes using  $TiCl_4$

S. No	Ar	R <sup>1</sup>	Phenol	Product	Time (min)	Yield (%) <sup>[a]</sup>	m.p [b] (°C)
1	C <sub>6</sub> H <sub>5</sub>	-CN	1-Naphthol	4a	15	91	205 <sup>16</sup>
2	2-Cl-C <sub>6</sub> H <sub>4</sub>	-CN	1-Naphthol	4b	15	89	235 <sup>16</sup>
3	3-Cl-C <sub>6</sub> H <sub>4</sub>	-CN	1-Naphthol	4c	20	87	220 <sup>16</sup>
4	4-Cl-C <sub>6</sub> H <sub>4</sub>	-CN	1-Naphthol	4d	10	91	229 <sup>11</sup>
5	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	-CN	1-Naphthol	4e	30	83	215 <sup>16</sup>
6	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	-CN	1-Naphthol	4f	45	84	216 <sup>11</sup>
7	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	-CN	1-Naphthol	4g	35	89	236 <sup>16</sup>
8	4-OH-C <sub>6</sub> H <sub>4</sub>	-CN	1-Naphthol	4h	10	92	245 <sup>11</sup>
9	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	-CN	1-Naphthol	4i	10	90	184 <sup>11</sup>
10	C <sub>6</sub> H <sub>5</sub>	-CN	2-Naphthol	4j	10	90	274 <sup>16</sup>
11	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub>	-CN	2-Naphthol	4k	10	93	255 <sup>16</sup>
12	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	-CN	2-Naphthol	4l	25	75	187 <sup>16</sup>
13	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	-CN	2-Naphthol	4m	12	83	191 <sup>11</sup>
14	2-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	-CN	2-Naphthol	4n	07	82	115 <sup>16</sup>
15	2-Cl-C <sub>6</sub> H <sub>4</sub>	-CN	2-Naphthol	4o	20	78	260 <sup>11</sup>
16	C <sub>6</sub> H <sub>5</sub>	-COOEt	2-Naphthol	4p	05	95	165
17	4-F-C <sub>6</sub> H <sub>4</sub>	-COOEt	2-Naphthol	4q	10	88	237
18	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	-COOEt	2-Naphthol	4r	20	85	248
19	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	-COOEt	2-Naphthol	4s	15	86	213
20	2-Cl-C <sub>6</sub> H <sub>4</sub>	-COOEt	2-Naphthol	4t	10	87	246

[a]Isolated yields; [b]The melting points are carried in open capillaries and are uncorrected.

derivatives. However it was observed that the aldehydes with electron withdrawing groups (NO<sub>2</sub>, halides) require longer reaction time to give the product.

## EXPERIMENTAL

Ethyl-2-amino-4-phenyl-4H-benzo[g]chromene-3-carboxylate (**4p**).

A mixture of benzaldehyde (1 mol) ethylcyanoacetate (1 mol), β-naphthol (1 mol) and  $TiCl_4$  (10 mol %) was stirred for 5 minutes at room temperature (monitored by TLC). The mixture was extracted with ethyl acetate and was washed with water. The organic layer was dried over  $Na_2SO_4$  and concentrated to give crude product, which is purified by column. (2:8 Ethyl acetate: Hexane).

**4p.** ir (KBr,  $cm^{-1}$ ): 3404, 3296, 2989, 2938, 2904, 1671, 1615, 1525, 1402, 1306, 1219, 1072, 825, 815, 743. <sup>1</sup>H nmr (300MHz,  $CDCl_3$ ): δ, 1.41 (3H, t, J=7.2Hz,  $CH_3$ ), 4.28 (2H, q,  $CH_2$ ), 5.64 (1H, s, CH), 6.35 (2H, brs,  $NH_2$ ), 7.10-8.08 (11H, m, Ar-H). Mass M. wt (345): M<sup>+</sup>, 346.4, 317.4 (M-C<sub>2</sub>H<sub>5</sub>), 300.4 (M-C<sub>2</sub>H<sub>5</sub> &-  $NH_2$ ).

*Anal.* Calcd for  $C_{22}H_{19}NO_3$ : C, 76.50; H, 5.54; N, 4.06. Found: C, 76.48; H, 5.50; N, 4.10%.

**4q.** ir (KBr,  $cm^{-1}$ ): 3404, 3191, 2924, 2716, 2209, 1716, 1610, 1549, 1496, 1407, 1299, 1276, 1128, 1080, 754. <sup>1</sup>H nmr (300MHz,  $CDCl_3$ ): δ, 1.33 (3H, t, J=9Hz,  $CH_3$ ), 3.90 (2H, q,  $CH_2$ ), 7.42-9.74 (10H, m, Ar-H), 7.28 (2H, brs,  $NH_2$ ), 9.10 (1H, s, CH).

*Anal.* Calcd for  $C_{22}H_{18}FNO_3$ : C, 72.72; H, 4.99; F, 5.23; N, 3.85. Found: C, 72.68; H, 5.01; F, 5.20; N, 3.89%.

**4r.** ir (KBr,  $cm^{-1}$ ): 3468, 3332, 3095, 3016, 1682, 1600, 1524, 1436, 1404, 1353, 1305, 1276, 1251, 1220, 1069, 822, 721. <sup>1</sup>H nmr (300MHz,  $CDCl_3$ ): δ, 1.29 (3H, t, J=7.5Hz,  $CH_3$ ), 4.02 & 4.37 (2H, m,  $CH_2$ ), 6.45 (2H, brs,  $NH_2$ ), 6.58 (1H, s, CH), 7.14-8.72 (10H, m, Ar-H).

*Anal.* Calcd for  $C_{22}H_{18}N_2O_5$ : C, 67.69; H, 4.65; N, 7.18. Found: C, 67.65; H, 4.68; N, 7.16%.

**4s.** ir (KBr,  $cm^{-1}$ ): 3418, 3305, 3207, 2979, 2958, 2933, 2831, 1660, 1627, 1612, 1515, 1504, 1456, 1407, 1371, 1310, 1262, 1243, 1227, 1159, 1098, 1061, 805, 792. <sup>1</sup>H nmr (300MHz,  $CDCl_3$ ): δ, 1.20 (3H, t, J=6Hz,  $CH_3$ ), 3.49 (3H, s,  $OCH_3$ ), 4.06 (2H, q,  $CH_2$ ), 4.83 (1H, s, CH), 6.36 (2H, brs,  $NH_2$ ), 6.47-7.26 (10H, m, Ar-H).

*Anal.* Calcd for  $C_{23}H_{21}NO_4$ : C, 73.58; H, 5.64; N, 3.73. Found: C, 73.55; H, 5.66; N, 3.80%.

**4t.** ir (KBr,  $cm^{-1}$ ): 3403, 3293, 2998, 2977, 2956, 1667, 1519, 1401, 1221, 1074, 740. <sup>1</sup>H nmr (300MHz,  $CDCl_3$ ): δ, 1.29 (3H, t, J=7.2Hz,  $CH_3$ ), 4.27 (2H, q,  $CH_2$ ), 6.02 (1H, s, CH), 6.42 (2H, brs,  $NH_2$ ), 6.99-8.36 (10H, m, Ar-H).

*Anal.* Calcd for  $C_{22}H_{18}ClNO_3$ : C, 69.57; H, 4.78; Cl, 9.33; N, 3.69. Found: C, 69.56; H, 4.75; Cl, 9.31; N, 3.71%.

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