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Efficient Synthesis of Benzo[*g*]- and Benzo[*h*]chromene Derivatives by One-Pot Three-Component Condensation of Aromatic Aldehydes with Active Methylene Compounds and Naphthols*

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Abstract—A convenient procedure is reported for the synthesis of benzo[*g*]- and benzo[*h*]chromene derivatives via one-pot three-component condensation of aromatic aldehydes with malononitrile or ethyl cyanoacetate and 1- or 2-naphthol in the presence of 10 mol % of titanium tetrachloride as catalyst. The reactions require no solvent; they are characterized by simple experimental procedure and easy isolation and can be performed on enlarged scale.

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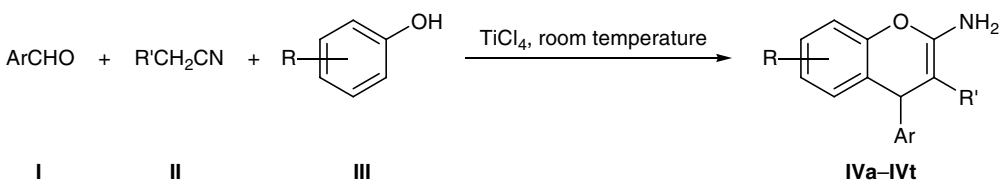
Any new procedure for the synthesis of required compounds should fit the principle of ideal synthesis as maximally as possible. According to Wender [1], an ideal synthesis is that ensuring one-step preparation of a target product in quantitative yield from readily accessible and inexpensive starting materials; in addition, it should be environmentally safe.

Benzopyran derivatives exhibit diverse pharmacological activity depending on the nature and position of substituents in their molecules. Benzopyran system constitutes a structural fragment of many natural products [2] which are widely distributed in the plant kingdom and are important due to their biological activity [3–6]. Compounds of the benzopyran series are used as food additives, cosmetic agents, pigments [7], fragrant substances, optical bleachers, fluorescent disperse dyes, and tunable laser dyes [8]. In the recent years, compounds exhibitng anticoagulant, antianaphylactic, spasmodic, diuretic, antibacterial, antifungal, insecticide, and anticarcinogenic activity [9], as well as potential biodegradable agrochemicals [10], were found among benzopyran derivatives.

Many known procedures for the synthesis of benzopyran derivatives involve three-component condensation of an active methylene compound, aromatic aldehyde, and activated phenol in the presence of a base [11]. However, the application of some of these methods is limited due to poor yields and laborious workup procedure. Titanium(IV) chloride was reported as a good catalyst for such processes as reduction [12], esterification [13], hydroamination [14], and others [15]. On the other hand, there are no published data on the synthesis of polyfunctionalized benzopyran derivatives in the presence of $TiCl_4$. In the present communication we describe a general and highly effective synthetic route to benzopyran derivatives using inex-

Scheme 1.



I **II** **III** **IVa–IVt**

For Ar, R, and R', see table.

* The text was submitted by the authors in English.

Yields of benzo[*g*]- and benzo[*h*]chromenes **IVa–IVt** in the three-component condensation of substituted benzaldehydes, malononitrile or ethyl cyanoacetate, and 1- or 2-naphtol

Compound no.	Ar	R^1	RC_6H_4OH	Reaction time, min	Yield,[a] %	mp, °C
IVa	C_6H_5	CN	1-Naphthol	15	91	205 [16]
IVb	2-ClC_6H_4	CN	1-Naphthol	15	89	235 [16]
IVc	3-ClC_6H_4	CN	1-Naphthol	20	87	220 [16]
IVd	4-ClC_6H_4	CN	1-Naphthol	10	91	229 [11]
IVe	2,4-$Cl_2C_6H_3$	CN	1-Naphthol	30	83	215 [16]
IVf	3-$O_2NC_6H_4$	CN	1-Naphthol	45	84	216 [11]
IVg	4-$O_2NC_6H_4$	CN	1-Naphthol	35	89	236 [16]
IVh	4-HO_6H_4	CN	1-Naphthol	10	92	245 [11]
IVi	4-$MeOC_6H_4$	CN	1-Naphthol	10	90	184 [11]
IVj	C_6H_5	CN	2-Naphthol	10	90	274 [16]
IVk	4-MeC_6H_4	CN	2-Naphthol	10	93	255 [16]
IVl	4-$O_2NC_6H_4$	CN	2-Naphthol	25	75	187 [16]
IVm	4-$MeOC_6H_4$	CN	2-Naphthol	12	83	191 [11]
IVn	2-$MeOC_6H_4$	CN	2-Naphthol	7	82	115 [16]
IVo	2-ClC_6H_4	CN	2-Naphthol	20	78	260 [11]
IVp	C_6H_5	COOEt	2-Naphthol	5	95	165
IVq	4-FC_6H_4	COOEt	2-Naphthol	10	88	237
IVr	2-$O_2NC_6H_4$	COOEt	2-Naphthol	20	85	248
IVs	4-$MeOC_6H_4$	COOEt	2-Naphthol	15	86	213
IVt	2-ClC_6H_4	COOEt	2-Naphthol	10	87	246

[a] Yield of the isolated product.

pensive and commercially available titanium tetrachloride as catalyst under solvent-free conditions.

According to the proposed procedure, a mixture of aromatic aldehyde **I**, active methylene compound **II** (malononitrile or ethyl cyanoacetate), activated phenol **III** (1- or 2-naphthol), and $TiCl_4$ (10 mol %) was stirred at room temperature until the reaction was complete (Scheme 1). The product was extracted into appropriate solvent, the extract was dried and concentrated, and the residue was purified by recrystallization. The reaction times and yields of substituted benzochromenes **IVa–IVf** are given in table. It is seen that the nature of substituent in the initial reactants does not affect the yield of the condensation products to a considerable extent. In all cases, the yields of **IVa–IVf** were fairly high (75–95%). Some increase in the reaction time may be noted for aromatic aldehydes containing electron-withdrawing groups (e.g., NO_2).

EXPERIMENTAL

The melting points were determined in open capillary and are uncorrected.

Ethyl 2-amino-4-phenyl-4*H*-benzo[*g*]chromene-3-carboxylate (IVp). A mixture of 1 mol of benzaldehyde, 1 mol of ethyl cyanoacetate, 1 mol of 2-naphthol, and 0.1 mol (10 mol %) of $TiCl_4$ was stirred for 5 min at room temperature. The progress of the reaction was monitored by TLC. When the reaction was complete, the mixture was extracted with ethyl acetate, the extract was washed with water and dried over anhydrous sodium sulfate, the solvent was removed, and the residue was recrystallized from ethanol. IR spectrum, ν, cm^{-1}: 3404, 3296, 2989, 2938, 2904, 1671, 1615, 1525, 1402, 1306, 1219, 1072, 825, 815, 743. ^1H NMR spectrum, δ, ppm: 1.41 t (3H, CH_3), 4.28 q (2H, CH_2), 5.64 s (1H, CH), 6.35 br.s (2H,

NH_2), 7.10–8.08 m (11H, H_{arom}). Mass spectrum, *m*/*z*: 346.4 $[M]^+$, 317.4 $[M - C_2H_5]^+$, 300.4 $[M - C_2H_5 - NH_2]^+$. Found, %: 76.48; H 5.50; N 4.10. $C_{22}H_{19}NO_3$. Calculated, %: C 76.50; H 5.54; N 4.06. *M* 345.

Compounds **IVa–IVo** and **IVq–IVt** were synthesized in a similar way.

Ethyl 2-amino-4-(4-fluorophenyl)-4*H*-benzo[*g*]-chromene 3-carboxylate (IVq). IR spectrum, ν, cm^{-1}: 3404, 3191, 2924, 2716, 2209, 1716, 1610, 1549, 1496, 1407, 1299, 1276, 1128, 1080, 754. ^1H NMR spectrum, δ, ppm: 1.33 t (3H, CH_3), 3.90 q (2H, CH_2), 7.42–9.74 m (10H, H_{arom}), 7.28 br.s (2H, NH_2), 9.10 s (1H, CH). Found, %: C 72.68; H 5.01; F 5.20; N 3.89. $C_{22}H_{18}FNO_3$. Calculated, %: C 72.72; H 4.99; F 5.23; N 3.85.

Ethyl 2-amino-4-(2-nitrophenyl)-4*H*-benzo[*g*]-chromene-3-carboxylate (IVr). IR spectrum, ν, cm^{-1}: 3468, 3332, 3095, 3016, 1682, 1600, 1524, 1436, 1404, 1353, 1305, 1276, 1251, 1220, 1069, 822, 721. ^1H NMR spectrum, δ, ppm: 1.29 t (3H, CH_3), 4.02 m and 4.37 m (2H, CH_2), 6.45 br.s (2H, NH_2), 6.58 s (1H, CH), 7.14–8.72 m (10H, H_{arom}). Found, %: C 67.65; H 4.68; N 7.16. $C_{22}H_{18}N_2O_5$. Calculated, %: C 67.69; H 4.65; N 7.18.

Ethyl 2-amino-4-(4-methoxyphenyl)-4*H*-benzo-[*g*]chromene-3-carboxylate (IVs). IR spectrum, ν, 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. ^1H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3), 3.49 s (3H, OCH_3), 4.06 q (2H, CH_2), 4.83 s (1H, CH), 6.36 br.s (2H, NH_2), 6.47–7.26 m (10H, H_{arom}). Found, %: C 73.55; H 5.66; N 3.80. $C_{23}H_{21}NO_4$. Calculated, %: C 73.58; H 5.64; N 3.73.

Ethyl 2-amino-4-(4-chlorophenyl)-4*H*-benzo-[*g*]chromene-3-carboxylate (IVt). IR spectrum, ν, cm^{-1}: 3403, 3293, 2998, 2977, 2956, 1667, 1519, 1401, 1221, 1074, 740. ^1H NMR spectrum, δ, ppm: 1.29 t (3H, CH_3), 4.27 q (2H, CH_2), 6.02 s (1H, CH), 6.42 br.s (2H, NH_2), 6.99–8.36 m (10H, H_{arom}). Found, %: C 69.56; H 4.75; Cl 9.31; N 3.71. $C_{22}H_{18}ClNO_3$. Calculated, %: C 69.57; H 4.78; Cl 9.33; N 3.69.

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