An Efficient and Chemoselective *Knoevenagel*/Hemiketalization Process for the Synthesis of New 2*H*-Chromenes in a One-Pot Three-Component Reaction

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A novel L-proline-catalyzed mild and ecological approach towards the synthesis of 2*H*-chromene derivatives was achieved by *Knoevenagel* reaction followed by an intramolecular hemiketalization process. In the present protocol, chemoselectivity has been successfully achieved by using L-proline as catalyst. This eco-friendly and chemoselective reaction provided an alternative synthetic method to prepare previously unknown 2*H*-chromene derivatives in a one-pot reaction.

Introduction. – 2*H*-Chromenes are an important class of oxygenated heterocyclic units found in various biologically active molecules (*Fig.*). The structural scaffolds of 2*H*-chromene exhibit various biological activities such as antiallergic [1], antiviral [2], antifungal [3], anti-inflammatory [4], anti-HIV [5], antidiabetic [6], and anticancer [7] effects. In particular, 2-aryl/alkyl substituted 2*H*-chromenes [8] are of significant interest in medicinal chemistry.

Amino acids are efficient, bi-functional, abundant, and inexpensive organocatalysts, which are widely used in several organic reactions [9], such as enantioselective, regioselective, and chemoselective reactions. Particularly, L-proline [10] was used in various organic transformations, such as *Mannich*, *Knoevenagel*, and *Michael* type reactions, by CO activation through enamine-iminium-ion intermediate formation. Proline can act as an acid or a base and can also assist chemical transformations, similar to enzymatic catalysis [11].

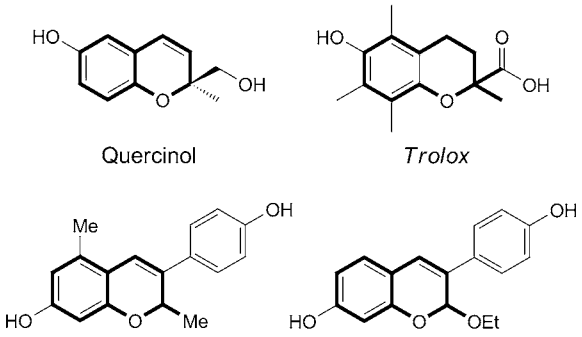
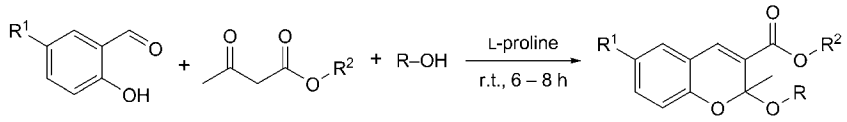


Figure. *Some biologically active compounds*

Multicomponent reactions [12] (MCRs) have an advantageous position among other reactions owing to the atom economy, convergent character, and simple procedures.

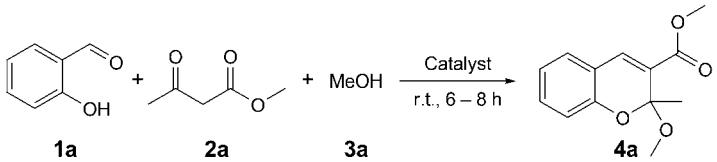
Several methods were reported for *Knoevenagel* condensation followed by an intramolecular transesterification process [13], whereas only few methods were reported for the synthesis of 2*H*-chromenes *via* intramolecular hemiketalization [14]. To the best of our knowledge, no chemoselective method for the reaction between salicylaldehyde and β-keto esters to synthesize 2-alkoxy-, or 2-alkyl-substituted 2*H*-chromenes in a one-pot reaction has been described. Therefore, the development of new and more general methods for the synthesis of 2,2′-disubstituted 2*H*-chromenes is of significant interest. In continuation of our research in the development of new and convenient methodologies [15], herein we wish to report a novel chemoselective method (*Scheme 1*) for the synthesis of new functionalized 2*H*-chromenes.

Scheme 1. *A One-Pot Reaction for the Synthesis of 2-Alkoxy-2*H*-chromenes*



Results and Discussion. – With the intention of finding a suitable catalyst, initially we started the model reaction of salicyladehyde (**1a**) with methyl acetoacetate (**2a**) in H_2O at 100°. The reaction did not proceed even after stretching the reaction time to 24 h. Other acid catalysts, such as TsOH, $Sc(OTf)_3$, $InCl_3$, $FeCl_3$, H_3BO_3, and *Amberlyst-15*, also failed to initiate the reaction. However, in the presence of base catalysts like DABCO, DBU, DIPEA, piperidine, TEA, and K_2CO_3 under different reaction conditions, 2-hydroxychromenes were obtained in low yields. The reaction was further improved by using L-proline as a catalyst (*Table 1*). The reaction of salicylaldehyde (**1a**) with methyl acetoacetate (**2a**) in MeOH (**3a**) in the presence of L-proline was completed within 6 h, and the alkoxychromene **4a**, was isolated in 75% yield. The product was characterized by spectral data and confirmed as methoxychromene, which showed that MeOH had acted as nucleophile. L-Thiaproline produced the required chromene product with significantly lower yield in compared to L-proline. Further, we examined *N*-substituted proline, but the yields were not satisfactory. By all these observations, we concluded that L-proline is the most suitable catalyst for the *Knoevenagel* condensation followed by intramolecular hemiketalization to synthesize novel chromene derivatives. Then, the study was planned to screen different concentrations of catalyst, such as 5, 10, 20, 30, 40 mol-%. It turned out that 30 mol-% of L-proline was best suited for the synthesis of chromene products. Increased molar ratios of proline did not affect the total yield. Then, we focussed on the reactivity of differently substituted salicylaldehydes and found that the unsubstituted salicylaldehyde reacted smothly with the β-keto ester to give a good yield (75%, **4a**). On the other hand, halogen (Br, Cl) substituted aldehydes gave even better yields (81%, **4i**) than

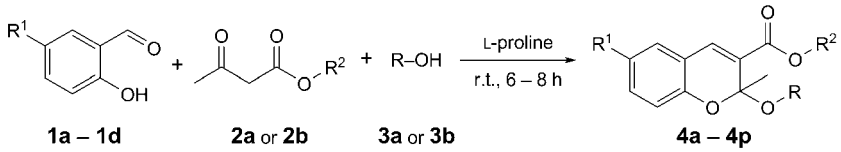
Table 1. *Screening of Catalysts for the Synthesis* 2H-*Chromene* (**4a**)[a])



Entry	Catalyst (30 mol-%)	Time [h]	Total yield [%][b])
1	L-Proline	6	75
2	L-Glycine	8	51
3	L-Phenylalanine	9	48
4	L-Lysine	12	–
5	L-Histadine	12	–
6	L-Glutamic acid	12	25
7	L-Aspartic acid	10	33
8	L-Thiaproline	9	45

[a]) Reaction conditions: **1a** (1mmol), **2a** (1 mmol), **3a** (2 ml), catalyst (30 mol-%), r.t., 8 h. [b]) Refers to isolated **4a** after column chromatography.

Table 2. *Scope of Substrates for the Synthesis of* 2H-*Chromenes*[a])[b])



Product	R	R^1	R^2	Time [h]	Yield [%]
4a	Me	H	Me	6	75
4b	Et	H	Me	7	73
4c	Me	H	Et	6	70
4d	Et	H	Et	7	68
4e	Me	Cl	Me	6	79
4f	Et	Cl	Me	7	77
4g	Me	Cl	Et	6	74
4h	Et	Cl	Et	7	72
4i	Me	Br	Me	6	81
4j	Et	Br	Me	7	79
4k	Me	Br	Et	6	76
4l	Et	Br	Et	7	74
4m	Me	NO_2	Me	7	71
4n	Et	NO_2	Me	8	69
4o	Me	NO_2	Et	7	66
4p	Et	NO_2	Et	8	64

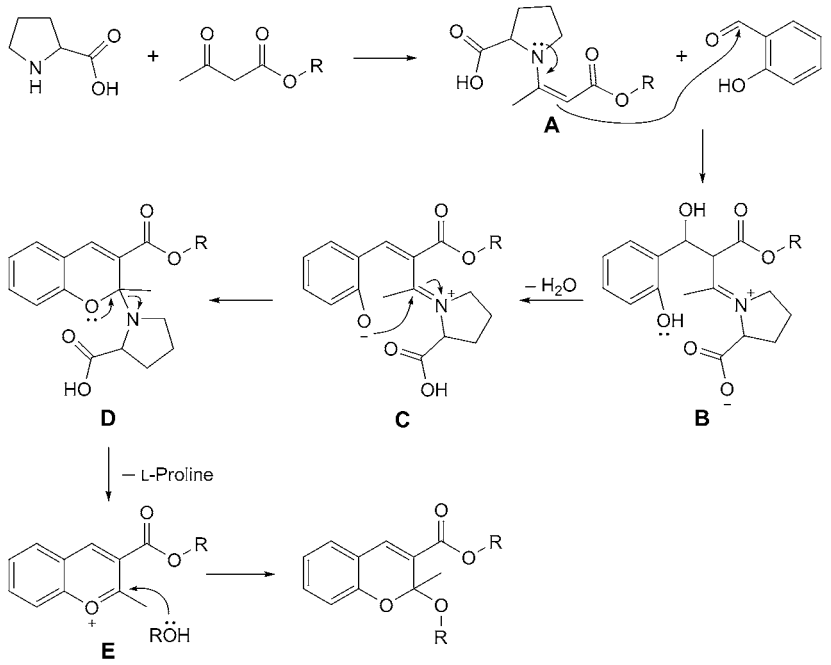
[a]) Salicylaldehyde (1 mmol), β-keto ester (1 mmol), and L-proline (30 mol-%), in alcohol (2 ml). [b]) Yield of the isolated pure product.

unsubstituted salicylaldehyde, whereas electron-withdrawing group-subsitituted aldehydes produced comparatively low yields (64%, **4p**). Further, we extended our study to screen various β-keto esters (*Table 2*).

We noticed that methyl acetoacetate (**2a**) reacted faster than ethyl acetoacetate (**2b**) and gave comparatively better yields (79%, **4e**), whereas long-chain and branched alkyl-substituted β-keto esters produced hydroxychromenes instead of alkoxychromenes due to steric hindrance. Next, we studied the reactivity of alchohols, and found slightly better results with MeOH (**3a**) than with EtOH (**3b**), for the reason that MeOH is sterically less hindered than EtOH. Further, we screened long-chain alchohols and branched alchohols; the reaction is proceeding well, but is limited to the formation of 2-hydroxychromenes. Steric hindrance and poor stability of alkoxychromenes cause the reaction to stop on the stage of hydroxychromenes.

The L-proline-catalyzed reaction proceeds *via* an enamine intermediate **A**. Intermediate **A** reacts with salicylaldehyde to give intermediate **B**, which undergoes dehydration to give intermediate **C**, which then undergoes cyclization to form the more stable benzopyrilium cation intermediate **E**. In this intermediate nucleophilic attack at the C(2) is favored. Attack of the alcohol at C(2) leads to the formation of the desired alkoxychromene (*Scheme 2*).

Scheme 2. *Plausible Mechanistic Pathway*



Conclusion. – In summary, we have developed an L-proline-catalyzed *Knoevenagel* condensation followed by hemiketalization for the synthesis of new 2*H*-chromenes

[17]. The present method provides a general route for the preparation of medicinally interesting 2*H*-chromenes in high yield. Such a 2*H*-chromene framework with diverse functionality provides an additional functional handle for further transformations, which can be utilized in the preparation of a library of compounds of pharmaceutical significance.

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Experimental Part

General. Salicyladehydes, β-keto esters, L-proline, and all solvents were obtained from local suppliers. Column chromatography (CC): silica gel (SiO_2; 60–120 mesh). M.p.: *Mettler-Temp* apparatus; uncorrected. IR Spectra: *PerkinElmer-1600* FT-IR spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker-Avance-300* and *500* spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard; *J* in Hz. ESI-MS: *VG Micromass 7070 H* spectrometer with a direct inlet system; in *m*/*z* [rel. %], and *Agilent 6510* Q-TOF LC/MS instrument.

General Procedure. In a typical experiment, the salicylaldehyde (1 mmol), methyl acetoacetate (1 mmol), and L-proline (30 mol-%) in MeOH (2 ml) were placed in a 10 ml round-bottom flask and stirred for 6 h at r.t. After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the crude product was purified by CC using AcOEt/hexane. All compounds were characterized by (NMR, MS, and IR) spectral data. Further, we have performed the reaction up to 5-g scales.

*Methyl 2-Methoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4a**). Yellow oil. IR: 3038, 2977, 2942, 2890, 1717, 1626, 1572, 1485, 1376, 1263, 1212, 1046, 915, 751. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (*s*, 1 H); 7.28–7.36 (*m*, 1 H); 7.21–7.26 (*m*, 1 H); 6.93–7.00 (*m*, 2 H); 3.84 (*s*, 3 H); 3.26 (*s*, 3 H); 1.95 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.0; 153.8; 136.2; 132.4; 128.7; 123.6; 121.4; 118.4; 115.9; 101.1; 51.9; 50.2; 25.5. ESI-MS: 257 ($[M+Na]^+$), 203 ($[M-MeO]^+$).

*Methyl 2-Ethoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4b**). Yellow oil. IR: 3039, 2978, 2941, 2891, 1715, 1627, 1571, 1487, 1374, 1265, 1212, 1044, 917, 748. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.70 (*s*, 1 H); 7.28–7.32 (*m*, 1 H); 7.22 (*dd*, *J* = 1.5, 6.0, 1 H); 6.92–6.97 (*m*, 2 H); 3.83 (*s*, 3 H); 3.48–3.56 (*m*, 2 H); 1.94 (*s*, 3 H); 1.12 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.1; 153.9; 136.1; 132.3; 128.7; 124.1; 121.2; 118.4; 115.8; 101.1; 58.4; 51.9; 26.2; 15.3. ESI-MS: 271 ($[M+Na]^+$), 203 ($[M-EtO]^+$).

*Ethyl 2-Methoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4c**). Yellow oil. IR: 3039, 2976, 2939, 2890, 1714, 1629, 1574, 1489, 1371, 1269, 1215, 1048, 919, 748. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.72 (*s*, 1 H); 7.21–7.35 (*m*, 2 H); 6.93–6.99 (*m*, 2 H); 4.23–4.35 (*m*, 2 H); 3.26 (*s*, 3 H); 1.95 (*s*, 3 H); 1.36 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.5; 153.7; 135.9; 132.2; 128.7; 121.4; 118.5; 115.9; 101.2; 60.8; 50.2; 25.5; 14.2. ESI-MS: 271 ($[M+Na]^+$), 217 ($[M-MeO]^+$).

*Ethyl 2-Ethoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4d**). Semi-solid. IR: 3040, 2979, 2940, 2892, 1716, 1628, 1571, 1483, 1375, 1264, 1213, 1048, 916, 748. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.69 (*s*, 1 H); 7.19–7.33 (*m*, 2 H); 6.90–6.99 (*m*, 2 H); 4.29 (*q*, *J* = 7.0, 2 H); 3.46–3.58 (*m*, 2 H); 1.95 (*s*, 3 H); 1.35 (*t*, *J* = 7.00, 3 H); 1.12 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.5; 153.8; 135.7; 132.1; 128.6; 124.4; 121.2; 118.4; 115.7; 101.1; 60.7; 58.3; 26.2; 15.3; 14.2. ESI-MS: 285 ($[M+Na]^+$), 217 ($[M-EtO]^+$).

*Methyl 6-Chloro-2-methoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4e**). Semi-solid. IR: 2976, 2935, 2896, 1717, 1626, 1565, 1479, 1374, 1264, 1210, 1044, 885, 817. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.63 (*s*, 1 H); 7.15–7.30 (*m*, 2 H); 6.90 (*d*, *J* = 8.5, 1 H); 3.84 (*s*, 3 H); 3.26 (*s*, 3 H); 1.94 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.6; 152.1; 134.7; 131.9; 127.9; 126.2; 125.0; 119.7; 117.4; 101.2; 52.0; 50.2; 25.1. ESI-MS: 291 ($[M+Na]^+$), 237 ($[M-MeO]^+$).

*Methyl 6-Chloro-2-ethoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4f**). Semi-solid. IR: 2974, 2938, 2891, 1715, 1629, 1564, 1477, 1370, 1267, 1215, 1048, 889, 815. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.60 (*s*, 1 H);

7.18–7.27 (*m*, 2 H); 6.88 (*d*, *J* = 8.5, 1 H); 3.83 (*s*, 3 H); 3.45–3.57 (*m*, 2 H); 1.93 (*s*, 3 H); 1.11 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.7; 152.2; 134.6; 131.8; 127.8; 126.0; 125.5; 119.8; 117.3; 101.2; 58.4; 52.0; 25.8; 15.2. ESI-MS: 305 ($[M+Na]^+$), 237 ($[M-EtO]^+$).

*Ethyl 6-Chloro-2-methoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4g**). Semi-solid. IR: 2977, 2939, 2892, 1718, 1627, 1566, 1471, 1371, 1267, 1211, 1043, 882, 819. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.62 (*s*, 1 H); 7.15–7.28 (*m*, 2 H); 6.90 (*d*, *J* = 8.5, 1 H); 4.25–4.34 (*m*, 2 H); 3.26 (*s*, 3 H); 1.94 (*s*, 3 H); 1.36 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.2; 152.1; 134.4; 131.8; 127.9; 126.2; 125.5; 119.8; 117.3; 101.3; 61.0; 50.2; 25.2; 14.2. ESI-MS: 305 ($[M+Na]^+$), 251 ($[M-MeO]^+$).

*Ethyl 6-Chloro-2-ethoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4h**). Semi-solid. IR: 2976, 2935, 2896, 1716, 1630, 1568, 1477, 1373, 1267, 1210, 1047, 883, 817. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.59 (*s*, 1 H); 7.19–7.27 (*m*, 2 H); 6.88 (*d*, *J* = 8.3, 1 H); 4.29 (*q*, *J* = 6.8, 2 H); 3.45–3.57 (*m*, 2 H); 1.94 (*s*, 3 H); 1.35 (*t*, *J* = 6.8, 3 H); 1.11 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.2; 152.1; 134.4; 131.8; 127.9; 126.2; 125.5; 119.8; 117.3; 101.3; 61.0; 50.2; 25.2; 14.2. ESI-MS: 319 ($[M+Na]^+$), 251 ($[M-EtO]^+$).

*Methyl 6-Bromo-2-methoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4i**). Semi-solid. IR: 2928, 1718, 1628, 1565, 1475, 1371, 1262, 1215, 1058, 874, 822. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.62 (*s*, 1 H); 7.38 (*dd*, *J* = 2.4, 8.5, 1 H); 7.35 (*d*, *J* = 2.4, 1 H); 6.85 (*d*, *J* = 8.5, 1 H); 3.83 (*s*, 3 H); 3.25(*s*, 3 H); 1.94 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.6; 152.6; 134.7; 133.0; 130.8; 124.9; 120.3; 118.6; 117.8; 101.2; 52.1; 50.2; 25.2. ESI-MS: 335 ($[M+Na]^+$), 281 ($[M-MeO]^+$).

*Methyl 6-Bromo-2-ethoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4j**). Semi-solid. IR: 2926, 1716, 1625, 1563, 1476, 1370, 1264, 1216, 1055, 875, 824. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.60 (*s*, 1 H); 7.38 (*dd*, *J* = 2.4, 8.5, 1 H); 7.35 (*d*, *J* = 2.3, 1 H); 6.83 (*d*, *J* = 8.5, 1 H); 3.83 (*s*, 3 H); 3.47–3.54 (*m*, 2 H); 1.93 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.7; 152.8; 134.7; 134.5; 130.8; 125.5; 120.3; 117.7; 113.1; 101.2; 58.5; 52.0; 25.9; 15.3. ESI-MS: 349 ($[M+Na]^+$), 281 ($[M-EtO]^+$).

*Ethyl 6-Bromo-2-methoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4k**). Semi-solid. IR: 2927, 1715, 1626, 1564, 1475, 1369, 1263, 1212, 1059, 877, 825. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.61 (*s*, 1 H); 7.39 (*dd*, *J* = 2.3, 8.5, 1 H); 7.36 (*d*, *J* = 2.4, 1 H); 6.85 (*d*, *J* = 8.5, 1 H); 4.25–4.33 (*m*, 2 H); 3.25 (*s*, 3 H); 1.94 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.2; 152.6; 134.7; 134.4; 130.8; 125.4; 120.4; 117.8; 113.3; 101.4; 61.0; 50.2; 25.9; 15.3. ESI-MS: 349 ($[M+Na]^+$), 295 ($[M-MeO]^+$).

*Ethyl 6-Bromo-2-ethoxy-2-methyl-2*H-*chromene-3-carboxylate* (**4l**). Semi-solid. IR: 2929, 1717, 1627, 1563, 1475, 1368, 1266, 1214, 1057, 873, 823. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.59 (*s*, 1 H); 7.38 (*dd*, *J* = 2.4, 8.5, 1 H); 7.35 (*d*, *J* = 2.4, 1 H); 6.83 (*d*, *J* = 8.5, 1 H); 4.29 (*q*, *J* = 7.2, 2 H); 3.47–3.55 (*m*, 2 H); 1.93 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.7; 152.8; 134.7; 134.5; 130.8; 125.5; 120.3; 117.7; 113.1; 101.2; 58.5; 52.0; 25.9; 15.3. ESI-MS: 363 ($[M+Na]^+$), 295 ($[M-EtO]^+$).

*Methyl 2-Methoxy-2-methyl-6-nitro-2*H-*chromene-3-carboxylate* (**4m**). White solid. M.p. 66–68°. IR: 3088, 2977, 2956, 1719, 1615, 1525, 1348, 1273, 1227, 1093, 1052, 955, 875. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.21 (*dd*, *J* = 2.6, 8.9, 1 H); 8.18 (*d*, *J* = 2.6, 1 H); 7.75 (*s*, 1 H); 7.05 (*d*, *J* = 8.9, 1 H); 3.87 (*s*, 2 H); 3.28 (*s*, 3 H); 1.99 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.1; 158.4; 141.9; 134.0; 127.5; 126.1; 124.4; 118.3; 116.6; 102.8; 52.3; 50.5; 25.5. ESI-MS: 302 ($[M+Na]^+$), 248 ($[M-MeO]^+$).

*Methyl 2-Ethoxy-2-methyl-6-nitro-2*H-*chromene-3-carboxylate* (**4n**). White solid. M.p. 72–74°. IR: 3089, 2979, 2952, 1719, 1617, 1523, 1344, 1272, 1221, 1092, 1058, 952, 876. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.20 (*dd*, *J* = 2.6, 8.9, 1 H); 8.17 (*d*, *J* = 2.6, 1 H); 7.71 (*s*, 1 H); 7.02 (*d*, *J* = 8.9, 1 H); 3.86 (*s*, 3 H); 3.53 (*q*, *J* = 7.0, 2 H); 1.98 (*s*, 3 H); 1.14 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 164.1; 158.4; 141.9; 134.0; 127.5; 126.1; 124.4; 118.3; 116.6; 102.8; 52.3; 50.5; 25.5. ESI-MS: 316 ($[M+Na]^+$), 248 ($[M-EtO]^+$).

*Ethyl 2-Methoxy-2-methyl-6-nitro-2*H-*chromene-3-carboxylate* (**4o**). White solid. M.p. 68–70°. IR: 3086, 2975, 2958, 1718, 1617, 1524, 1345, 1273, 1223, 1095, 1056, 953, 874. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.17–8.24 (*m*, 2 H); 7.74 (*s*, 1 H); 7.05 (*d*, *J* = 8.9, 1 H); 4.26–4.38 (*m*, 2 H); 3.28 (*s*, 3 H); 1.99 (*s*, 3 H); 1.38 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 163.6; 158.4; 141.9; 133.7; 127.4; 126.3; 124.4; 118.4; 116.6; 102.8; 61.3; 50.5; 25.5; 14.1. ESI-MS: 316 ($[M+Na]^+$), 262 ($[M-MeO]^+$).

*Ethyl 2-Ethoxy-2-methyl-6-nitro-2*H-*chromene-3-carboxylate* (**4p**). White solid. M.p. 74–76°. IR: 3087, 2979, 2954, 1718, 1615, 1526, 1349, 1274, 1228, 1094, 1053, 956, 876. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.17–8.21 (*m*, 2 H); 7.70 (*s*, 1 H); 7.02 (*d*, *J* = 8.6, 1 H); 4.32 (*q*, *J* = 7.2, 2 H); 3.50–3.56 (*m*, 2 H); 1.98 (*s*,

3 H); 1.38 (*t*, *J* = 7.2, 3 H); 1.14 (*t*, *J* = 7.2, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 163.6; 158.6; 141.7; 133.5; 127.3; 126.8; 124.4; 118.3; 116.5; 102.8; 61.2; 58.9; 26.1; 15.1; 14.1. ESI-MS: 330 ($[M + Na]^+$), 262 ($[M - EtO]^+$).

REFERENCES

[1] E. E. Schweizer, D. Meeder-Nycz, in 'Chromenes, Chromanes, Chromones', Ed. G. P. Ellis, Wiley-Interscience, NewYork, 1977, p. 11; W. S. Bowers, T. Ohta, J. S. Cleere, P. A. Marsella, *Science* **1976**, *193*, 542; J. Hepworth, 'Comprehensive Heterocyclic Chemistry', Eds. A. R. Katritzky, C. W. Rees, Pergamon, Oxford, 1984, Vol. 3, p. 737.

[2] N. De Meyer, A. Haemers, L. Mishra, H. K. Pandey, L. A. C. Pieters, D. A. Vanden Berghe, A. J. Vlietinck, *J. Med. Chem*. **1991**, *34*, 736.

[3] K. Mori, G. Audran, H. Monti, *Synlett* **1998**, 259.

[4] J.-J. Chen, T.-Y. Wang, T.-L. Hwang, *J. Nat. Prod.* **2008**, *71*, 212; P. Gebhardt, K. Dornberger, F. A. Gollmick, U. Gräfe, A. Härtl, H. Görls, B. Schlegel, C. Hertweck, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2558.

[5] N. Iwata, N. Wang, X. Yao, S. Kitanaka, *J. Nat. Prod*. **2004**, *67*, 1106; H. Hu, T. J. Harrison, P. D. Wilson, *J. Org. Chem*. **2004**, *69*, 3782.

[6] R. Korec, K. H. Sensch, T. Zoukas, *Arzneim. Forsch*. **2000**, *50*, 122.

[7] F. Cassidy, M. J. Evan, M. S. Hadley, A. H. Haladij, P. E. Leach, G. Stemp, *J. Med. Chem.* **1992**, *35*, 1623.

[8] N. Ishizuka, K. Matsumura, K. Sakai, M. Fujimoto, S. Mihara, T. Yamamori, *J. Med. Chem*. **2002**, *45*, 2041; R. M. Tripathi, S. S. Bisht, V. P. Pandey, S. K. Pandey, S. Singh, S. K. Sinha, V. Chaturvedi, *Med. Chem. Res.* **2011**, *20*, 1515; J. L. Wang, K. Aston, D. Limburg, C. Ludwig, A. E. Hallinan, F. Koszyk, B. Hamper, D. Brown, M. Graneto, J. Talley, T. Maziasz, J. Masferrer, J. Carter, *Bioorg. Med. Chem. Lett*. **2010**, *20*, 7164.

[9] A. Bassan, W. Zou, E. Reyes, F. Himo, A. Córdova, *Angew. Chem., Int. Ed*. **2005**, *44*, 7028; A. Kumar, Akanksha, *Tetrahedron* **2007**, *63*, 11086; P. Dziedzic, A. Córdova, *Tetrahedron Asymmetry* **2007**, *18*, 1033; F. S. Prout, *J. Org. Chem*. **1953**, *18*, 928.

[10] X. Wang, Y. Zhang, H. Tan, Y. Wang, P. Han, D. Z. Wang, *J. Org. Chem*. **2010**, *75*, 2403; K. Xu, S. Zhang, Y. Hu, Z. Zha, Z. Wang, *Chem. – Eur. J.* **2013**, *19*, 3573; Z. An, Y. Guo, L.-W. Zhao, Z. Li, J. He, *ACS Catal.* **2014**, *4*, 2566.

[11] S. Balalaie, M. Bararjanian, A. M. Amani, B. Movassagh, *Synlett* **2006**, 263; P. Kotrusz, S. Toma, *Arkivoc* **2006**, *v*, 100; J. Mabry, B. Ganem, *Tetrahedron Lett*. **2006**, *47*, 55; S. Chandrasekhar, K. Vijeender, K. V. Reddy, *Tetrahedron Lett*. **2005**, *46*, 6991; S. Chandrasekhar, C. Narsihmulu, N. R. K. Reddy, S. S. Sultana, *Tetrahedron Lett*. **2004**, *45*, 4581; T. Darbre, M. Machuqueiro, *Chem. Commun*. **2003**, *9*, 1090.

[12] M. B. Steffensen, D. Rotem, H. Bayley, *Nat. Chem.* **2014**, *6*, 603; F. Damkaci, A. Szymaniak, *J. Chem. Educ.* **2014**, *91*, 943; S. G. Dawande, V. Kanchupalli, B. S. Lad, J. Rai, S. Katukojvala, *Org. Lett.* **2014**, *16*, 3700; D. J. Lee, H. S. Han, J. Shin, E. J. Yoo, *J. Am. Chem. Soc.* **2014**, *136*, 11606; V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Soc. Rev.* **2014**, *43*, 4633.

[13] C.-H. Wang, Z. Guan, Y.-H. He, *Green. Chem*. **2011**, *13*, 2048; R. H. Vekariya, H. D. Patel, *Synth. Commun*. **2014**, *44*, 2756; R. Roy, S. Rakshit, T. Bhowmik, S. Khan, A. Ghatak, S. Bhar, *J. Org. Chem*. **2014**, *79*, 6603; L. V. Frolova, I. Malik, P. Y. Uglinskii, S. Rogelj, A. Kornienko, I. V. Magedov, *Tetrahedron Lett.* **2011**, *52*, 6643.

[14] F. Yang, Z. Wang, H. Wang, H. Zhang, H. Yue, L. Wang, *RSC Adv.* **2014**, *4*, 25633; B. C. Raju, G. Saidachary, J. A. Kumar, *Tetrahedron* **2012**, *68*, 6289; B. C. Raju, G. Saidachary, J. A. Kumar, B. Sridhar, *Helv. Chim. Acta* **2011**, *94*, 248; C. Xu, G. Yang, C. Wang, S. Fan, L. Xie, Y. Gao, *Molecules* **2013**, *18*, 11964; D. L. Chizhov, V. Y. Sosnovskikh, M. V. Pryadeina, Y. V. Burgart, V. I. Saloutin, V. N. Charushin, I. Y. Postovsky, *Synlett* **2008**, 281; X. He, Z. Yan, X. Hu, Y. Zuo, C. Jiang, L. Jin, Y. Shang, *Synth. Commun*. **2014**, *44*, 1507; J. Andrieux, C. Vidal, G. Adam, M. Plat, D. Molho, *Bull. Soc. Chim. Fr.* **1982**, *9*, 309.

[15] L. C. Rao, H. M. Meshram, N. S. Kumar, N. N. Rao, N. J. Babu, *Tetrahedron Lett.* **2014**, *55*, 1127; L. C. Rao, N. S. Kumar, N. J. Babu, H. M. Meshram, *Tetrahedron Lett.* **2014**, *55*, 5342; P. B. Thakur, H. M. Meshram, *RSC Adv.* **2014**, *4*, 6019; P. B. Thakur, H. M. Meshram, *RSC Adv.* **2014**, *4*, 5343; B. M. Babu, G. S. Kumar, P. B. Thakur, V. M. Bangade, H. M. Meshram, *Tetrahedron Lett.* **2014**, *55*, 3473.

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