The first ionic liquid-promoted Kabbe condensation reaction for an expeditious synthesis of privileged bis-spirochromanone scaffolds

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ABSTRACT

A variety of privileged bis-spirochromanones were synthesized for the first time from 4,6-diacetyl resorcinol in one-pot by carrying out the Kabbe condensation in room temperature ionic liquid [bbim]Br.

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1. Introduction

Chromone derivatives,[1] in particular 2-spiro-chroman-4(1H)-ones are ubiquitous in nature and possess various biological activities which include antiarrhythmic,[2] anti-HIV,[3] antidiabetic,[4] ACC inhibitor,[5] vanilloid receptor antagonist,[6] growth hormone secretagogues,[7] histamine receptor antagonist,[8] and antiviral.[9] Furthermore, these 2-spiro-chroman-4(1H)-ones serve as an important precursor for the synthesis of other medicinally important compounds such as rotenoids[10] and xanthones.[11] Recently, these structural scaffolds have been assigned as privileged structures for drug development.[12]

During the last few years, the concept of bivalency or homodimer strategy (i.e., combination into a single molecule of two identical structural entities or fragments of well known biologically active natural products or synthetic drugs) has emerged as a powerful tool in the medicinal chemistry research to improve either the overall potency of the parent compounds or could result in an entirely new complementary biological activity.[13] Although, there are numerous homodimers of chromones such as bis-flavones, bis-coumarins, and bis-flavanones whose biological activities are well documented,[14] there are no attempts made so far, to synthesize bis-2-spirochromanone scaffolds despite their propitious biological functions. Intrigued by these facts, we surmised whether a library of bis-spirochromanones could be synthesized conveniently for biological testing (Scheme 1).

Kabbe condensation between enamine and 2-hydroxy acetophenone is a commonly employed method for the construction of 2-spirochromanone skeleton.[15] The other two general approaches are: (1) the cross aldol condensation of lithium enolate of 2-hydroxy acetophenone with ketone, followed by dehydration[16] (2) Mukaiyama aldol condensation of bis-silyl enol ether derived from 2-hydroxy acetophenone with ketone, followed by acidic ring closure.[17] Although these methods have wide utility, often they suffer due to multi-step processes,[16,17] tedious work-up, and the usage of stoichiometric quantities of Lewis acids such as $BF_3 \cdot Et_2O$, $SnCl_4$, $AlCl_3$, and $TiCl_4$.[17] In the context of our ongoing research program dealing with drug discovery, we were encountered with a need for an efficient methodology for the synthesis of bis-spirochromanone libraries and we were interested in exploring the possibility of conducting the Kabbe condensation reaction in ionic liquids. Applications of ionic liquids in chemical processes have blossomed only within the last decade and they have been used successfully for a variety of organic transformations.[18] We herein describe an extremely facile and environmentally friendly synthesis of bis-2-spirochromanones in one-pot by carrying out Kabbe condensation in an ionic liquid [bbim]Br catalyzed by morpholine.

2. Results and discussion

Initially, the Kabbe condensation of 4,6-diacetyl resorcinol **1** with cyclohexanone **2a** was chosen as a model and the influence of various ionic liquids and bases was examined to find the optimal conditions for the reaction. The results are summarized in Table 1.
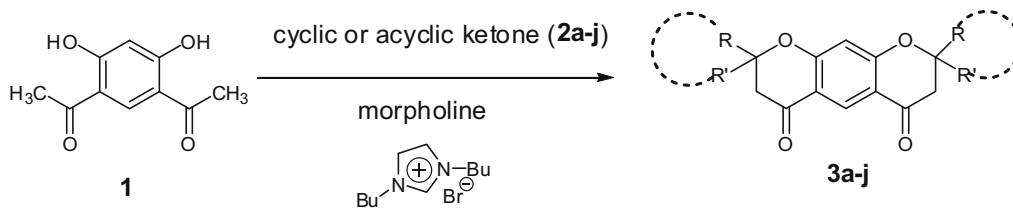
Scheme 1.

Table 1
Screening the optimized reaction conditions for Kabbe condensation of 4,6-diacetyl resorcinol (**1**) with cyclohexanone (**2a**)[a]
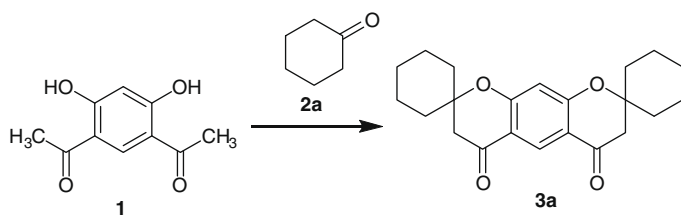
Entry	Ionic liquid	Base	Yield[b] (%)
1	[bbim]PF$_6$	Pyrrolidine	20
		L-Proline	32
		Morpholine	30
2	[bmim]Br	Pyrrolidine	40
		L-Proline	40
		Morpholine	50
3	[bbim]Br	Pyrrolidine	50
		L-Proline	65
		Morpholine	80
4	[Hbim]ClO$_4$	L-Proline	24
		Morpholine	20
5	[Hbim]Br	L-Proline	15
		Morpholine	<10

[a] Reaction conditions: **1** (2.5 mmol), **2a** (5.5 mmol), base (5.5 mmol) in ionic liquid (**2g**) 95–100 °C for 12 h.
[b] Yields were isolated and unoptimized.

As can be seen from Table 1, the ionic liquid [bbim]Br was found to be most effective for this transformation providing 80% yield of the desired product (Table 1, entry 3). Moreover, the nature of a base also has a pronounced impact on the reaction, morpholine appears to be better than pyrrolidine and L-proline. On further modification of the reaction conditions, we were delighted to find that the usage of stoichiometric quantity of morpholine was not necessary; only catalytic amount was sufficient to effect this transformation efficiently. It is noteworthy to mention here that utilization of weakly basic morpholine as a catalyst in organic transformation has not been explored much in the literature except in a recent report by Wu et al.[19] Thus, in a typical experiment, treatment of 4,6-diacetyl resorcinol (1 equiv) with cyclohexanone (2.2 equiv) in ionic liquid [bbim]Br with catalytic amount of morpholine (0.5 equiv) at 95 °C for 8 h afforded the corresponding bis-spirochromanone **3a** in 80% yield.

The product **3a** was characterized using standard spectroscopic techniques. In the IR spectrum, a signal corresponding to the chromanone carbonyl was observed at 1701 cm^{-1}. The signal corresponding to the C3 protons of chromanone skeleton was observed at δ 2.68 ppm in the ^{1}H NMR spectrum and the corresponding ^{13}C resonance signal was observed at δ 47.8 ppm. In the ^{13}C NMR spectrum, the spirocarbon was discernible at δ 81.0 ppm. Conclusive evidence for its structure was obtained from single-crystal X-ray analysis (Fig. 1).[20,21]

Using the optimized conditions in hand, we subjected a series of cyclic and acyclic ketones for this modified Kabbe condensation protocol to explore the generality and scope of the process and the results are summarized in Table 2. The results indicate that the enolizable cyclic ketones (**2b–g**) were successfully reacted with
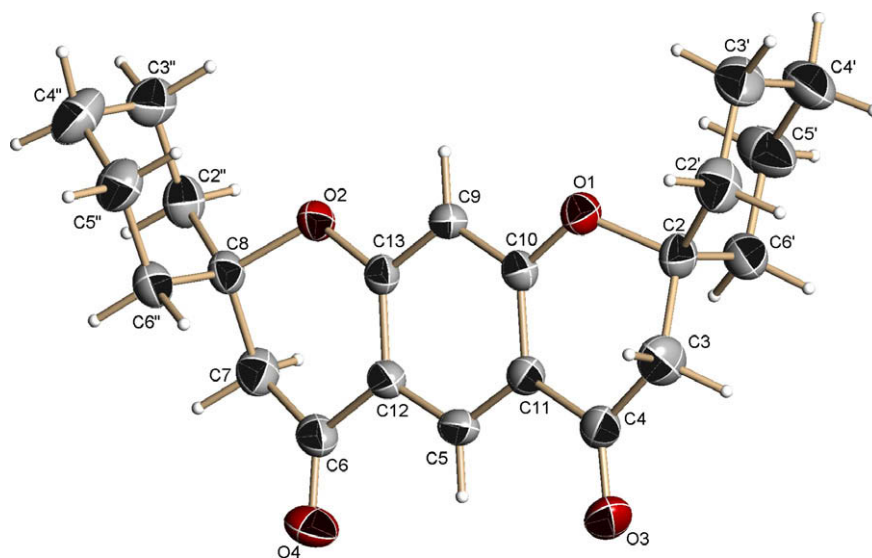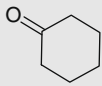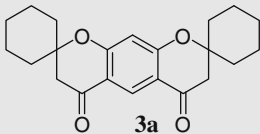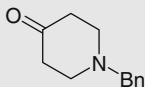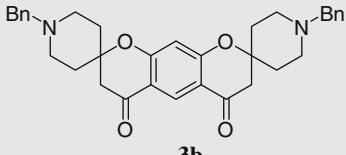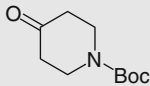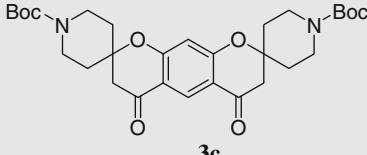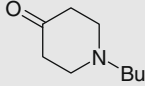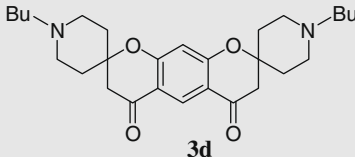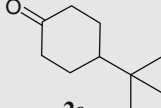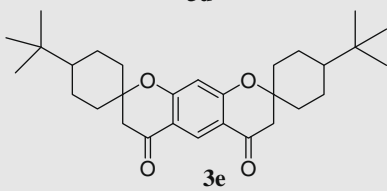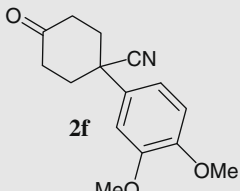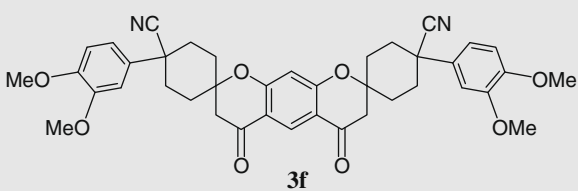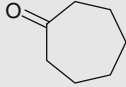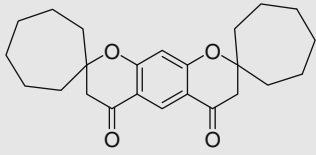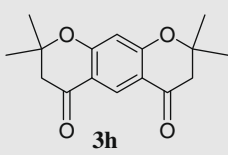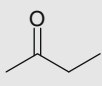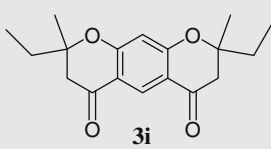

Figure 1. ORTEP structure of compound **3a**.
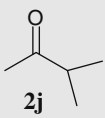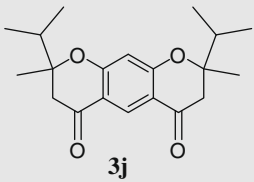
Table 2
Reaction of 4,6-diacetyl resorcinol with various cyclic and acyclic ketones

Entry	Ketone	Product 3[a]	Time (h)	Yield[b] (%)
1	2a	3a	8	80
2	2b	3b	8	75
3	2c	3c	9	78
4	2d	3d	12	55
5	2e	3e	12	72
6	2f	3f	12	58
7	2g	3g	12	61
8	2h	3h	8	84[d]
9	2i	3i	10	74

Table 2 (continued)

Entry	Ketone	Product 3[a]	Time (h)	Yield[b] (%)
10	2j	3j	12	70
11	2k	3k	12	82[d]
12	2l	n.r.[c]		
13	2m	n.r.[c]		

[a] All the products were characterized by spectroscopic data.
[b] Yields were isolated and unoptimized.
[c] n.r. = No reaction.
[d] Known compounds.

4,6-diacetyl resorcinol under this procedure, providing moderate to good yields of desired bis-spirochromanones (**3b–g**). The method is well amenable for acyclic ketones as well (Table 2, entries 8–10). However, with cyclopentanone (**2k**), the reaction was very sluggish and we could isolate only one side condensed product **3k** which may be attributed to the less reactive nature of the cyclopentanone ring. Non-enolizable ketones 4,4′-difluorobenzophenone (**2l**) and 4,4′-dichlorobenzophenone (**2m**) did not give any desired condensation products probably due to steric hindrance of the bulky phenyl groups.[17] It is noteworthy to mention here that the only known compound in the series **3h** was previously prepared using photo-Fries methodology in very poor yield,[22] in comparison to the 84% yield in the present one-pot procedure (Table 2, entry 8).

The role of the ionic liquid [bbim]Br in the Kabbe condensation may be attributed to its inherent Bronsted/Lewis acidity and high solvating ability.[23] Probably, the highly acidic 2H proton of [bbim]Br activates the carbonyl carbon of both alkanone and acetophenone, thus facilitates the enamine formation as well as the ready cyclization of unsaturated ketone intermediate **4** to the final product **3** (Fig. 2)
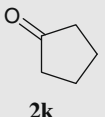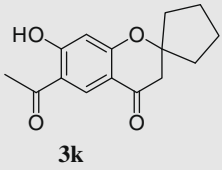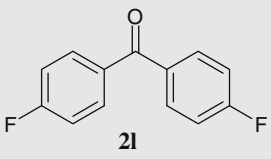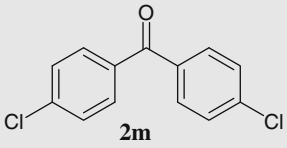
The advantage of the use of ionic liquid as a novel reaction medium for this Kabbe condensation is that this ionic liquid can be easily recovered and reused. The products can be easily separated from the ionic liquid medium by simple extraction with ethylacetate. We successfully reused this ionic liquid up to three runs without much loss of activity for a selected compound **3a** (run 1, 80%; run 2, 81%; run 3, 78%).

On comparison of our results with those in some of the published procedures,[16,17] we find that this protocol provides significant advantages in terms of mild reaction conditions, single-step, circumventing the use of stoichiometric quantities of Lewis acids, and reusability of ionic liquid.

In conclusion, we describe here a facile and environmentally benign synthesis of novel bis-spirochromanones by modifying Kabbe condensation using the advantage of ionic liquid as a solvent and promoter. Moreover, usage of catalytic quantity of inexpensive and weakly basic morpholine make this method more attractive. Easy workup, moderate to good isolated yield and reusability of ionic liquid makes this method simple for operation and useful to generate a vast array of bis-spirochromanone libraries for biological screening.

3. Experimental

3.1. Preparation of bis-spirochroman-4(1H)-ones; general procedure

A mixture of 4,6-diacetyl resorcinol (0.48 g; 2.5 mmol), ketone (5.5 mmol), and morpholine (1.2 mmol) was added to an ionic liquid [bbim]Br (**2g**)[23] and stirred at 95–100 °C for the time indi-
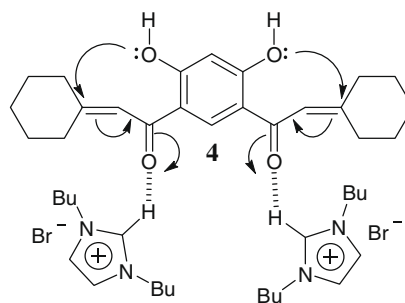

Figure 2.

cated in Table 2. After completion, (TLC; EtOAc/hexane, 1:3) the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined EtOAc extracts were concentrated in vacuo and the resulting product was directly charged on a small silica gel column and eluted with a mixture of 15% EtOAc/hexane to afford the pure bis-spirochromanone. The IL was solubilized in acetonitrile, treated with charcoal, and filtered. The filtrate was evaporated and the IL was dried under vacuum for further reuse. All products were characterized by IR, NMR, mass spectrometry, and elemental analysis. All new compounds gave satisfactory spectroscopic data in accordance with their structures.

Selected data for the new compounds:

3.1.1. Bis-spirochroman-4(1*H*)-one 3a (Table 2, entry 1)

White solid; mp 184–185 °C; IR (neat): 2940, 2853, 1701, 1641, 1605, 1561, 1482, 1429, 1362, 1338, 1210, 1070, 1022, 938, 914, 858 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.43–1.74 (m, 16H), 1.94–2.01 (m, 4H), 2.68 (br s, 4H), 6.50 (s, 1H, aromatic), 8.46 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.4, 164.9, 127.4, 115.5, 105.3, 81.0, 47.8, 34.8, 24.9, 21.3; ESI-MS: m/z = 355 [M+H]$^+$, 301, 183; Anal. Calcd for C$_{22}$H$_{26}$O$_4$: C, 74.55; H, 7.39. Found: C, 74.87; H, 7.14.

3.1.2. Bis-spirochroman-4(1*H*)-one 3b (Table 2, entry 2)

White solid; mp 100–101 °C; IR (neat): 3778, 3620, 3468, 3019, 2876, 2400, 1685, 1608, 1521, 1470, 1424, 1246, 1215, 1026, 966, 859 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.68–1.83 (m, 4H), 1.98–2.04 (m, 4H), 2.38–2.49 (m, 4H), 2.61–2.65 (m, 4H), 2.69 (br s, 4H), 3.54 (s, 4H), 6.56 (s, 1H, aromatic), 7.31 (m, 10H, aromatic), 8.46 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.0, 164.7, 138.1, 129.0, 128.2, 127.1, 115.8, 105.6, 79.2, 62.9, 48.6, 47.7, 34.5; ESI-MS: m/z = 537 [M+H]$^+$, 379, 263; Anal. Calcd for C$_{34}$H$_{36}$N$_2$O$_4$: C, 76.09; H, 6.76; N, 5.22. Found: C, 75.78; H, 7.05; N, 5.28.

3.1.3. Bis-spirochroman-4(1*H*)-one 3c (Table 2, entry 3)

White solid; mp 216–217 °C; IR (neat): 3019, 2978, 1687, 1608, 1559, 1470, 1368, 1343, 1247, 1215, 1158, 1027, 966, 860 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.46 (s, 18H), 1.62 (m, 4H), 1.97–2.05 (m, 4H), 2.71 (br s, 4H), 3.14–3.26 (m, 4H), 3.86–3.93 (m, 4H), 6.55 (s, 1H, aromatic), 8.50 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 189.4, 164.5, 154.6, 128.0, 115.9, 105.6, 79.9, 79.2, 63.3, 47.7, 34.2, 28.3; ESI-MS: m/z = 357 [M−Boc+H]$^+$; Anal. Calcd for C$_{30}$H$_{40}$N$_2$O$_8$: C, 64.73; H, 7.24; N, 5.03. Found: C, 64.79; H, 6.95; N, 4.98.

3.1.4. Bis-spirochroman-4(1*H*)-one 3d (Table 2, entry 4)

Semisolid; IR (neat): 3678, 3425, 3119, 2467, 2128, 1665, 1642, 1525, 1440, 1424, 1222, 1215, 1028, 966, 860 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.92 (t, J = 8 Hz, 6H), 1.31–1.54 (m, 8H), 1.94–2.04 (m, 8H), 2.51–2.65 (m, 8H), 2.71 (br s, 4H), 3.11 (m, 4H), 6.48 (s, 1H, aromatic), 8.38 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.5, 165.8, 129.2, 115.7, 105.6, 79.1, 56.2, 48.6, 47.2, 34.8, 30.2, 20.9, 13.1; Anal. Calcd for C$_{28}$H$_{40}$N$_2$O$_4$: C, 71.76; H, 8.60; N, 5.98. Found: C, 72.08; H, 8.21; N, 6.18.

3.1.5. Bis-spirochroman-4(1*H*)-one 3e (Table 2, entry 5)

White solid; mp 239–240 °C; IR (neat): 2949, 2867, 1699, 1606, 1557, 1469, 1366, 1299, 1241, 1185, 1138, 1009, 985, 936, 878, 855 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.87 (s, 18H), 1.60–1.79 (m, 14H), 2.06–2.12 (m, 4H), 2.83 (s, 4H), 6.39 (s, 1H, aromatic), 8.44 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.7, 164.9, 127.6, 115.7, 105.4, 80.4, 48.8, 46.9, 35.2, 32.37, 27.5, 21.9; ESI-MS: m/z = 467 [M+H]$^+$, 381, 300; Anal. Calcd for C$_{30}$H$_{42}$O$_4$: C, 77.21; H, 9.07. Found: C, 76.85; H, 9.22.

3.1.6. Bis-spirochroman-4(1*H*)-one 3f (Table 2, entry 6)

White solid; mp 169–170 °C; IR (neat): 3613, 2936, 2836, 2231, 1696, 1608, 1561, 1467, 1413, 1346, 1299, 1256, 1148, 1024, 984, 936, 850 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.98–2.31 (m, 16H), 2.78 (br s, 4H), 3.88 (s, 6H), 3.92 (s, 6H), 6.52 (s, 1H, aromatic), 6.89–7.03 (m, 6H, aromatic), 8.52 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.4, 165.6, 148.2, 147.3, 136.9, 127.8, 125.3, 119.6, 115.5, 112.3, 105.2, 81.2, 55.8, 47.3, 36.7, 34.2, 25.4; ESI-MS: m/z = 699 [M+Na]$^+$, 523, 458, 306; Anal. Calcd for C$_{40}$H$_{40}$N$_2$O$_8$: C, 70.99; H, 5.96; N, 4.14. Found: C, 70.67; H, 6.32; N, 3.96.

3.1.7. Bis-spirochroman-4(1*H*)-one 3g (Table 2, entry 7)

White solid; mp 141–142 °C; IR (neat): 3684, 3019, 2932, 2860, 2400, 1692, 1558, 1467, 1306, 1250, 1215, 1157, 1021, 928, 879 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.44–1.79 (m, 20H), 2.01–2.13 (m, 4H), 2.70 (br s, 4H), 6.44 (s, 1H, aromatic), 8.44 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.7, 165.3, 127.6, 115.6, 105.5, 85.5, 48.7, 38.5, 29.3, 21.9; ESI-MS: m/z = 383 [M+H]$^+$, 301, 275; Anal. Calcd for C$_{24}$H$_{30}$O$_4$: C, 75.36; H, 7.91. Found: C, 75.61; H, 7.72.

3.1.8. Bis-chroman-4(1*H*)-one 3i (Table 2, entry 9)

White solid; mp 123–124 °C; IR (neat): 3342, 2978, 1704, 1606, 1552, 1469, 1378, 1296, 1260, 1222, 1168, 1042, 1023, 911, 882, 836 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.97 (t, J = 4.0, 2.0 Hz, 6H), 1.69–1.84 (m, 4H), 2.61 (d, J = 6.0 Hz, 2H), 2.73 (d, J = 6.0 Hz, 2H), 6.39 (s, 1H, aromatic), 8.45 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.7, 165.4, 127.6, 115.3, 105.3, 82.6, 46.8, 32.4, 23.6, 7.8; HRMS (ESI): m/z calcd for C$_{18}$H$_{22}$O$_4$ [M]$^+$: 302.1518; found: 302.1360.

3.1.9. Bis-chroman-4(1*H*)-one 3j (Table 2, entry 10)

White solid; mp 125–126 °C; IR (neat): 2978, 1704, 1606, 1561, 1469, 1378, 1296, 1260, 1222, 1168, 1082, 1023, 930, 889, 856.cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.98 (d, J = 4 Hz, 6H), 1.01 (d, J = 4 Hz, 6H), 1.31 (s, 6H), 2.09 (m, 2H), 2.59 (d, J = 16 Hz, 2H), 2.82 (d, J = 16 Hz, 2H), 6.41 (s, 1H, aromatic), 8.46 (s, 1H, aromatic); ^{13}C NMR (50 MHz, CDCl$_3$): δ = 190.8, 165.3, 127.3, 115.2, 105.3, 85.1, 44.8, 35.7, 19.8, 17.2, 16.6; ESI-MS: m/z = 331 [M+H]$^+$; Anal. Calcd for C$_{20}$H$_{26}$O$_4$: C, 72.70; H, 7.93. Found: C, 72.94; H, 7.63.

Acknowledgements

References and notes

1. (a) Ellis, G. P. Chromenes, Chromanones and Chromones. In *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1977; Vol. 31, pp 11–139; (b) Hepworth, J.. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 3, pp 737–883.
2. Elliott, J. M.; Selnick, H. G.; Claremon, D. A.; Baldwin, J. J.; Buhrow, S. A.; Butcher, J. W.; Habecker, C. N.; King, S. W.; Lynch, J. J.; Phillips, B. T.; Ponticello, G. S.; Radzilowski, E. M.; Remy, D. C.; Stein, R. B.; White, J. I.; Young, M. B. *J. Med. Chem.* **1992**, *35*, 3973.
3. (a) Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Vilaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; Pezzuto, J. M.; Hughes, S. H.; Flavin, T. M.; Cibulski, M.; Boulanger, W. A.; Shone, R. L.; Xu, Z. Q. *J. Med. Chem.* **1996**, *39*, 1303; (b) Ishikawa, T.; Oku, Y.; Tanaka, T.; Kumamoto, T. *Tetrahedron Lett.* **1999**, *40*, 3777.
4. Oka, M.; Matsumoto, Y.; Sugiyama, S.; Tsuruta, N.; Matsushima, M. *J. Med. Chem.* **2000**, *43*, 2479.

5. Yamakawa, T.; Iona, H.; Niiyama, K.; Yamada, K.; Iino, T.; Ohkubo, M.; Imamura, H.; Shibata, J.; Kusunoki, J.; Yang, L. PCT Int. Appl. WO 2007/011809, **2007**; *Chem. Abstr.* **2007**, *146*, 184379.

6. Brown, B. S.; Koenig, J. R.; Gomtsyan, A. R.; Lee, C. H. PCT Int. Appl. WO 2007/121299, **2007**; *Chem. Abstr.* **2007**, *147*, 486435.

7. (a) Patchett, A. A.; Nargund, R. P.; Tata, J. R.; Chen, M. H.; Barakat, K. J.; Johnston, D. B. R.; Cheng, K.; Chan, W. W. S.; Butler, B.; Hickey, G.; Jacks, T.; Schleim, K.; Pong, S. S.; Chaung, L. Y. P.; Chen, H. Y.; Frazier, E.; Leung, K. H.; Chiu, S. H. L.; Smith, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 7001; (b) Yang, L. H.; Morriello, G.; Prendergast, K.; Cheng, K.; Jacks, T.; Chan, W. W. S.; Schleim, K. D.; Smith, R. G.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 107.

8. William, B. T.; Ralph, H. J. H.; Travis, W. PCT Int. Appl. WO 2007/088462, **2007**; *Chem. Abstr.* **2007**, *147*, 257665.

9. Nikolic, S.; Bartel, S.; Brands, M.; Niewohner, U.; Paessens, A.; Graef, E.; Schlemmer, K. H.; Henninger, K.; Endermann, R.; Weber, O.; Koletzki, D. U.S. Patent 2002/0082264, **2002**; *Chem. Abstr.* **2002**, *136*, 247491.

10. (a) Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Thomas, J. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 653; (b) Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Thomas, J. L. *Tetrahedron Lett.* **1998**, *39*, 881.

11. Singh, O. V.; Kapil, R. S.; Garg, C. P.; Kapoor, R. P. *Tetrahedron Lett.* **1991**, *32*, 5619.

12. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

13. (a) Tietze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996; (b) Deady, L. W.; Desneves, J.; Kaye, A. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *Bioorg. Med. Chem.* **2008**, *8*, 977; (c) Feng, S.; Wang, Z.; He, X.; Zheng, S.; Xia, Y.; Jiang, H.; Tang, X.; Bai, D. *J. Med. Chem.* **2005**, *48*, 655.

14. (a) Zembower, D. E.; Lin, Y. M.; Flavin, M. T.; Chen, F. C.; Korba, B. E. *Antiviral Res.* **1998**, *39*, 81; (b) Rahman, M.; Riaz, M.; Desai, U. R. *Chem. Biodivers.* **2007**, *4*, 2495. and references cited therein.

15. (a) Kabbe, H. J. *Synthesis* **1978**, 886; (b) Kabbe, H. J.; Widdig, A. *Angew Chem., Int. Ed. Engl.* **1982**, *21*, 247.

16. Banerji, A.; Goomer, N. C. *Tetrahedron Lett.* **1979**, *20*, 3685.

17. Kelly, S. E.; Vanderplas, B. C. *J. Org. Chem.* **1991**, *56*, 1325.

18. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3773; (c) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.

19. Wu, H.; Lu, L.; Shen, Y.; Wan, Y.; Yu, K. *Synth. Commun.* **2006**, *36*, 1193.

20. (a) The data on X-ray intensity of compound **3a** were collected on a Bruker SMART APEX CCD diffractometer with omega and phi scan mode, λ (Mo Kα) = 0.71073 Å at T = 293 (2) K. All the data were corrected for Lorentzian, polarization, and absorption effects using Bruker's SAINT and SADABS programs. The crystal structure was solved by direct methods using SHELXS-97 and the refinement was performed by full matrix least squares of F^2 using SHELXL-97. Hydrogen atoms were included in the refinement as per the riding model.; (b) Sheldrick, G. M. *SHELX-97 Program for Crystal Structure Solution and Refinement*; University of Göttingen: Germany, 1997.

21. The crystallographic data of compound **3a** has been deposited with the Cambridge Crystallographic Data Center as deposition No. CCDC 706278. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

22. Miranda, M. A.; Primo, J.; Tormos, R. *Heterocycles* **1988**, *27*, 673.

23. Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2003**, *44*, 1835. and references cited therein.