Bull. Chem. Soc. Ethiop. **2014**, 28(2), 289-294.
Printed in Ethiopia
DOI: http://dx.doi.org/10.4314/bcse.v28i2.12
ISSN 1011-3924

SHORT COMMUNICATION

REACTION OF ETHYL ACETOACETATE AND 2′-HYDROXYCHALCONES: EFFICIENT ROUTE TO 9-ARYL-6*H*-BENZO[*C*]CHROMEN-6-ONES

Ishmael B. Masesane* and Ofentse Mazimba

Department of Chemistry, University of Botswana, Private Bag 00704, Gaborone, Botswana

(Received April 19, 2013; revised November 15, 2013)

ABSTRACT. The reaction of ethyl acetoacetate and 2′-hydroxychalcones under atmospheric air to furnish a series of functionalized 6*H*-benzo[*c*]chromen-6-ones in moderate yields is reported. The reaction proceeds through *trans*-esterification, *intra*-molecular Michael addition, Robinson annulation and oxidative aromatization.

KEY WORDS: 2′-Hydroxychalcones, Ethyl acetoacetate, 6*H*-Benzo[*c*]chromen-6-ones, *Trans*-esterification, Michael addition, Robinson annulation, Oxidative aromatization

INTRODUCTION

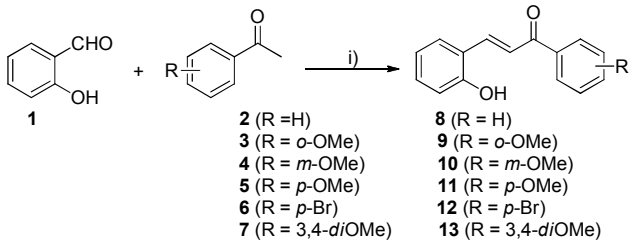
6*H*-Benzo[*c*]chromen-6-ones are an interesting class of coumarins that occur in a number of pharmacologically active natural products such as alternariol, automnariol and autumnariniol [1, 2]. These compounds and their analogs have been reported as specific inhibitors of the growth of endothelic cells and oestrogen receptors [3]. 6*H*-benzo[*c*]chromon-6-ones therefore represent core structures for the synthesis of pharmaceuticals.

A limited number of synthetic procedures have been reported for the synthesis of 6*H*-benzo[*c*]chromen-6-ones and these methods involves three or more steps, less accessible starting materials and the availability of chromones as starting material. These procedures include the [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 1-(silyloxy)alk-1-en-3-ones [4-6], reactions of 3-formylcoumarin with 1,3-bis(silylenol ethers) [7, 8], sequential [3+3] Suzuki cyclization reactions [9], Bu_3SnH mediated radical cyclisation [10], coupling of benzoic acid with benzoquinone using the electrophilic Ir(III) catalyst [11] and the reactions of chromones with 1,3-dicarbonyl compounds [12, 13]. There is, therefore, a need to develop synthetically useful methodologies for the preparation of 6H-benzo[*c*]chromen-6-ones using readily available starting materials. Thus, we describe in this paper a facile procedure for the synthesis of 9-phenyl-6*H*-benzo[*c*]chromen-6-ones involving the reaction of ethyl acetoacetate and chalcones derived from the condensation of salicylaldehyde and acetophenone derivatives.

RESULTS AND DISCUSSIONS

The conditions for the preparation of the 2′-hydroxychalcones were originally worked out by our group in connection with our approach to the synthesis of flavans [14]. Employing this known procedure, a series of 2′-hydroxychalcones **8**-**13** were prepared through the reaction of salicylaldehyde **1** and acetophenone derivatives **2**-**7** in excellent yields (Scheme 1).

*Corresponding author. E-mail: masesane@mopipi.ub.bw

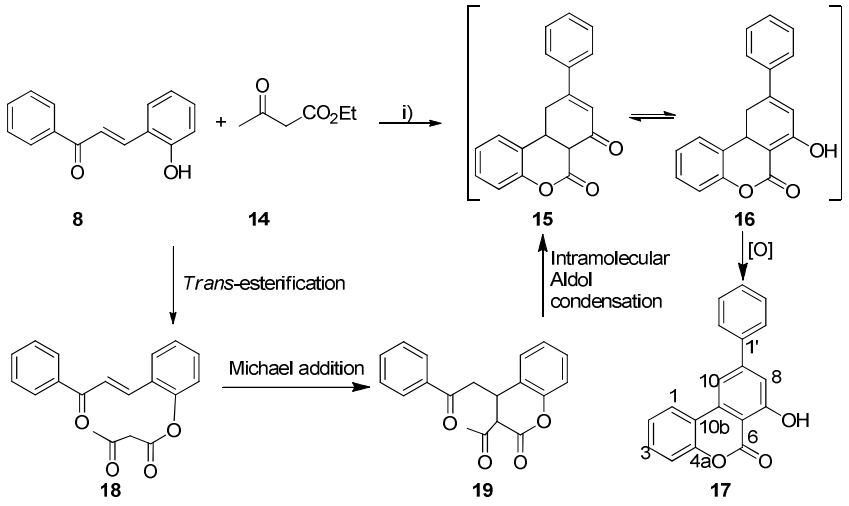


Scheme 1. Reagents and conditions: i) 50% NaOH (aq), EtOH, 60 ^{o}C, 2 h, **8** (88%), **9** (88%), **10** (86%), **12** (87%), **13** (86%).

With the required 2′-hydroxychalcones in hand, we were in a position to study their reactions with ethyl acetoacetate. To this end, a solution of the 2-hydroxychalcone **8** and ethyl acetoacetate **14** in CH_3OH in the presence of diethylamine was stirred at 60 ^{o}C and the reaction monitored by TLC. Workup by acidification using 4 M HCl and recrystalization of the resulting crude product from ethanol gave 6*H*-benzo[*c*]chromen-6-one **17** in 56% yield, Scheme 2. Alternatively, this reaction can also be mediated by K_2CO_3 or Et_2NH/K_2CO_3 (1:0.5 mole ratio) at room temperature to afford 6*H*-benzo[*c*]chromen-6-one **17** at 56% yields. The product was characterized on the basis of NMR experiments and the ^{1}H NMR peaks around δ11.33 (s) assigned to the chelated proton of the hydroxyl group and those resonating at δ7.34 (d) and δ7.82 (d) assigned to the *meta*-coupled H-8 and H-10 protons (^{3}J = 1.5 Hz) were found to be diagnostic.

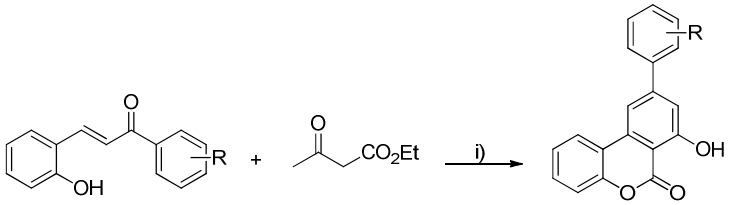
The Michael addition of active methylene compounds to chalcones is well documented [15-20]. On the basis of these precedents, the formation of chromenone **17** was thought to proceed by first a Michael addition of ethyl acetoacetate **14** to chalcone **8** followed by *intra*-molecular *trans*-esterification and intramolecular Aldol condensation to give intermediate **15**. In an effort to isolate intermediate 1**5**, the reaction of **8** and **14** was repeated under an atmosphere of nitrogen. Suprisingly, the *trans*-esterification product **18** was detected (by proton NMR) in the crude product instead of the Michael addition product. However, all attempts to purify **18** using column chromatography led to cyclisation and oxidative aromatization to give chromenone **17**. These results suggested that intermediate **18** was highly unstable species when exposed to atmospheric air. We thus propose that *trans*-esterification between acetoacetate **14** and hydroxychalcone **8** proceeds first to give ester **18** followed by an *intra*-molecular Michael addition to give coumarin **19** and finally an intramolecular Aldol condensation to afford dihydrochromenone **15** (Scheme 2).

Oxidative aromatization of intermediate **15** is the last reaction involved in the synthesis of chromenone **17**. It is instructive to note that there is precedent for atmospheric air mediated oxidative aromatization of cyclohexadienes [21]. In the context of intermediate **15**, a keto-enol tautomerization would proceed to give cyclohexadiene **16** which undergoes oxidative aromatization to afford chromenone **17** (Scheme 2).



Scheme 2. Reagents and conditions: i) Et_2NH, MeOH, 60 ^oC.

Employing the procedure described above, 2′-hydroxychalcone derivatives **9**, **10**, **11**, **12** and **13** were reacted with **14** to give 6*H*-benzo[c]chromen-6-ones **20**-**24** in 51-59% yields (Scheme 3). The methoxy and the bromo groups did not have any significant effect on the yields of this reaction.



9 (R = *o*-OMe)
10 (R = *m*-OMe)
11 (R = *p*-OMe)
12 (R = *p*-Br)
13 (R = 3,4-diOMe)

14

20 (R = *o*-OMe)
21 (R = *m*-OMe)
22 (R = *p*-OMe)
23 (R = *p*-Br)
24 (R = 3,4-diOMe)

Scheme 3. Reagents and Conditions: i) Et_2NH, MeOH, 60 ^oC, **20** (51%), **21** (57%), **22** (51%), **23** (59%), **24** (58%).

In conclusion, we have reported a facile synthesis of 6*H*-benzo[*c*]chromen-6-ones in moderate yields from the reactions of 2′-hydroxychalcones and ethyl acetoacetate. The procedure involves four reactions in one-pot and uses readily available starting materials.

EXPERIMENTAL

Representative Procedure. To a solution of 2′-hydroxychalcone **1** (0.54 g, 2.4 mmol) in CH_3OH (20 mL) was added diethylamine (0.71 g, 4.8 mmol). Ethyl acetoacetate (0.32 g, 2.4 mmol) was then added and the reaction mixture was stirred at 60 ^oC and was monitored by TLC. Upon completion of the reaction, the reaction mixture was acidified using hydrochloric acid (4 M) and the resulting precipitate was collected by filtration and recrystallized from ethanol to afford 7-hydroxy-9-phenyl-6*H*-benzo[c]chromen-6-one **17** as a white solid. Yield 56%, m.p. 211-213 ^oC. ν_{max} (neat) 2941, 1676, 1203, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.34 (1H, *d*, *J* = 1.5 Hz, H-8), 7.40 (1H, *dd*, *J* = 8.7, 1.5 Hz, H-3), 7.42 (1H, *d*, *J* = 8.7 Hz, H-4), 7.51 (1H, *m*, H-4′), 7.53 (1H, *dd*, *J* = 8.7, 1.8 Hz, H-3), 7.59 (2H, *dd*, *J* = 8.7, 2.1 Hz, H-3', 5'), 7.73 (2H, *dd*, *J* = 8.7, 2.1 Hz, H-2′, 6′,), 7.82 (1H, *d*, *J* = 1.5 Hz, H-10), 8.15 (1H, *d*, H-1, *J* = 8.1), 11.44 (1H, *s*, -OH); ^{13}C NMR (75 MHz, $CDCl_3$): 104.9 (C-6a), 111.1 (C-10), 115.0 (C-8), 117.8 (C-4), 118.4 (C-10b), 123.3 (C-1), 125.1 (C-3), 127.4 (C-2′ and 6′), 129.0 (C-4′), 129.1 (C-3′ and 5′), 130.7 (C-3), 135.5 (C-1′), 139.5 (C-10a), 150.3 (C-9), 150.8 (C-4a), 162.7(C-6), 165.3 (C-7). HRMS-EI: Found: M^+ 288.0790, $C_{20}H_{14}O_4$. Calcd. for m/z 288.0786.

7-Hydroxy-9-(2-methoxyphenyl)-6H-benzo[c]chromen-6-one ***20***. Yield 51%, white solid, m.p. 153-155 ^oC; ν_{max} (neat): 3077, 2924, 1667, 1274, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 3.78 (3H, *s*, -OCH_3), 6.98 (1H, *dd*, *J* = 8.7, 0.9 Hz, H-3′), 7.04 (1H, *dd*, *J* = 7.5, 0.9 Hz, H-5′), 7.19 (1H, *d*, *J* = 1.2 Hz, H-8), 7.25 (1H, *dd*, *J* = 8.1, 1.2 Hz, H-4′,), 7.30 (1H, *dd*, *J* = 7.8, 1.5 Hz, H-4), 7.32 (1H, *dd*, *J* = 7.8, 1.5 Hz, H-3), 7.34 (1H, *dd*, *J* = 7.2, 1.2 Hz, H-6′), 7.45 (1H, *ddd*, *J* = 8.1, 7.2, 1.5 Hz, H-2,), 7.68 (1H, *d*, *J* = 1.2 Hz, H-10), 8.00 (1H, *dd*, *J* = 8.1, 1.5 Hz, H-1), 11.26 (1H, *s*, -OH); ^{13}C NMR (75 MHz, $CDCl_3$): 55.7 (OMe), 104.7 (C-6a), 111.5 (C-3′), 113.8 (C-10), 117.7 (C-8), 117.8 (C-4), 118.6 (C-10b), 121.0 (C-5′), 123.4 (C-1), 125.1 (C-3), 129.0 (C-1′), 130.1 (C-2), 130.5 (C-4′), 130.6 (C-6′), 134.6 (C-10a), 148.2 (C-9), 150.7 (C-4a), 156.5 (C-2′), 161.9 (C-7), 165.4 (C-6);; HRMS-EI: found: M^+ 318.0895, $C_{20}H_{14}O_4$. Calcd. for m/z 318.0892.

7-Hydroxy-9-(3-methoxyphenyl)-6H-benzo[c]chromen-6-one ***21***. Yield 57%, white solid, m.p. 152-154 ^oC; ν_{max} (neat): 3076, 2924, 1683, 1205, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 3.83 (3H, *s*, -OCH_3), 6.93 (1H, *dt*, *J* = 7.2, 2.4, 0.9 Hz, H-4′), 7.15 (1H, *t*, *J* = 2.1 Hz, H-2′), 7.22 (1H, *dd*, *J* = 8.7, 2.4 Hz, H-6′), 7.23 (1H, *d*, *J* = 1.5 Hz, H-8), 7.28 (1H, *dd*, *J* = 7.2, 1.2 Hz, H-2), 7.31 (1H, *t*, *J* = 1.2 Hz, H-4), 7.38 (1H, *ddd*, *J* = 8.1, 7.8, 1.5 Hz, H-5′), 7.48 (1H, *ddd*, *J* = 8.4, 7.2, 1.5 Hz, H-3), 7.71 (1H, d, *J* = 1.5 Hz, H-10), 8.04 (1H, *dd*, *J* = 8.1, 1.5 Hz, H-1), 11.35 (1H, *s*, OH); ^{13}C NMR (75 MHz, $CDCl_3$): 55.4 (OMe), 105.0 (C-6a), 111.2 (C-10), 113.2 (C-2′), 114.3 (C-4′), 115.1 (C-8), 117.8 (C-4), 118.4 (C-10b), 119.8 (C-6′), 123.4 (C-1), 125.2 (C-2), 130.1 (C-5′), 130.7 (C-3), 135.5 (C-10a), 141.0 (C-1′), 150.2 (C-9), 150.8 (C-4a), 160.1 (C-3′), 162.3 (C-7), 165.3 (C-6); HRMS-EI: found: M^+ 318.0900, $C_{20}H_{14}O_4$. Calcd. for m/z 318.0892.

7-Hydroxy-9-(4-methoxyphenyl)-6H-benzo[c]chromen-6-one ***22***. Yield 51%, white solid, m.p. 236-238 ^oC; ν_{max} (neat): 3124, 2924, 1681, 1209, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 3.94 (3H, *s*, OCH_3), 7.08 (2H, *d*, *J* = 8.7 Hz, H-3′, 5′), 7.31 (1H, *d*, *J* = 1.5 Hz, H-8), 7.40 (1H, *dd*, *J* = 8.4, 1.2 Hz, H-2,), 7.43 (1H, *dd*, *J* = 8.1, 1.1 Hz, H-4), 7.54 (1H, *ddd*, *J* = 8.4, 8.1, 1.5 Hz, H-3), 7.70 (2H, *d*, *J* = 8.7 Hz, H-2′ and 6′), 7.81 (1H, *d*, *J* = 1.5 Hz, H-10), 8.16 (1H, *dd*, *J* = 8.1, 1.5 Hz, H-1), 11.40 (1H, *s*, -OH); ^{13}C NMR (75 MHz, $CDCl_3$): 55.4 (OMe), 104.4 (C-6a), 110.5 (C-10), 114.4 (C-8), 114.5 (C-3′ and 5′), 117.8 (C-4), 123.4 (C-1), 125.1 (C-2), 128.6 (C-2′ and 6′), 130.6 (C-3), 131.8 (C-1′), 135.4 (C-10b), 149.9 (C-10a), 150.8 (C-9), 160.6 (C-4a), 162.7 (C-7 and 4′), 165.4 (C-6); HRMS-EI: found: M^+ 318.0899, $C_{20}H_{14}O_4$. Calcd. for m/z 318.0892.

9-(4-Bromophenyl)-7-hydroxy-6H-benzo[c]chromen-6-one ***23***. Yield 59%, white solid, m.p. 202-204 ^{o}C; ν_{max} (neat): 3135, 2920, 1674, 1203, 1083 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 7.16 (1H, *d*, *J* = 1.2 Hz, H-8), 7.29 (1H, *dd*, *J* = 8.7, 1.5 Hz, H-4), 7.34 (1H, *dd*, *J* = 7.5, 1.5 Hz, H-2), 7.43 (1H, *dd*, *J* = 7.2, 1.5 Hz, H-3), 7.48 (2H, *d*, *J* = 8.7, 2.1 Hz, H-2′ and 6′), 7.56 (2H, *dd*, *J* = 8.7, 2.1 Hz, H-3′ and 5′), 7.66 (1H, *d*, *J* = 1.2 Hz, H-10), 8.05 (1H, *dd*, *J* = 8.1, 1.2 Hz, H-1), 11.33 (1H, *s*, -OH); ^{13}C NMR (75 MHz, $CDCl_3$): 105.2 (C-6a), 110.9 (C-10), 114.8 (C-8), 117.9 (C-4), 118.2 (C-4′), 123.4 (C-1), 123.5 (C-10b), 125.2 (C-2), 129.0 (C-2′ and 6′), 130.9 (C-3), 132.3 (C-3′ and 5′), 135.6 (C-1′), 138.4 (C-10a), 149.0 (C-9), 150.8 (C-4a), 162.7 (C-7), 165.2 (C-6); HRMS-EI: found: M^+ 365.9893 (99), M^++2 367.9875 (100), $C_{19}H_{11}BrO_3$. Calcd. for m/z 365.9892.

7-Hydroxy-9-(3,4-dimethoxyphenyl)-6H-benzo[c]chromen-6-one ***24***. Yield 58%, white solid, m.p. 148-150 ^{o}C; ν_{max} (neat): 3050, 2930, 1680, 1205, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 3.90 (3H, *s*, OCH_3), 3.93 (3H, *s*, OCH_3), 6.65 (1H, *br*, H-5′), 6.69 (1H, *dd*, *J* = 1.2 Hz, H-2′), 7.29 (1H, *d*, *J* = 1.2 Hz, H-8), 7.37 (1H, *dd*, *J* = 1.2 Hz, H-6′), 7.38 (1H, *ddd*, *J* = 8.7, 7.2, 1.2 Hz, H-3), 7.42 (1H, *dd*, *J* = 8.7, 1.2 Hz, H-4), 7.56 (1H, *ddd*, *J* = 8.1, 7.2, 1.5 Hz, H-2), 7.79 (1H, *d*, *J* = 1.2 Hz, H-10), 8.09 (1H, *dd*, *J* = 8.1, 1.2 Hz, H-1), 11.36 (1H, *s*, -OH); ^{13}C NMR (75 MHz, $CDCl_3$): 55.5 (OMe), 55.7 (OMe), 104.3 (C-6a), 99.2 (C-5′), 105.0 (C-2′), 113.6 (C-10), 117.4 (C-8), 117.7 (C-4), 118.7 (C-10b), 121.8 (C-10a), 123.4 (C-1), 125.0 (C-6′), 130.4 (C-2), 131.3 (C-3), 134.5 (C-1′), 148.0 (C-9), 150.7 (C-4′), 157.7 (C-3′), 161.5 (C-4a), 161.9 (C-7), 165.4 (C-6); HRMS-EI: found: M^+ 348.0993, $C_{21}H_{16}O_5$. Calcd. for m/z 348.0998.

ACKNOWLEDGEMENTS

We thank the Royal Society of Chemistry and the University of Botswana for financial support and Dr Sichilongo for mass spectrometry experiments.

REFERENCES

1. Saha, D.; Fetzner, R.; Burkhardt, B.; Podlech, J.; Metzler, M.; Dang, H.; Lawrence, C.; Fischer, R. *PLoS ONE* **2012**, 7, 1.
2. Koorbanally, C.; Neil, R.; Crouch, N.R.; Dulcie, A.; Mulholland, D.A. in *Phytochemistry: Advances in Research*, Imperato, F. (Ed.); Research Signpost: India; **2006**; pp 69-85.
3. Pandey, J.; Jha A.K.; Hajela, K. *Bioorg. Med. Chem.* **2004**, 12, 2239.
4. Ullah, E.; Appel, B.; Fischer, C.; Langer, P. *Tetrahedron* **2006**, 62, 9694.
5. Appel, B.; Saleh, N.N.R.; Langer, P. *Chem. Eur. J.* **2006**, 12, 1221.
6. Hussain, I.; Yawer, M.A.; Lau, M.; Pundt, T.; Fischer, C.; Görls, H.; Langer P. *Eur. J. Org. Chem.* **2008**, 503.
7. Fatunsin, O.; Iaroshenko, V.O.; Dudkin, S.; Mkrtchyan, S.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2010**, 51, 4693.
8. Langer, P.; Appel, B. *Tetrahedron Lett.* **2003**, 44, 5133.
9. Nguyen, V.T.H.; Langer, P. *Tetrahedron Lett.* **2005**, 46, 1013.
10. Bowman, W.R.; Mann, E.; Parr, J. *J. Chem. Soc*., *Perkin Trans. I*, **2000**, 2991.
11. Engelman, L.K.; Feng, Y.; Ison, E.A. *Organometallics* **2011**, 30, 4572.
12. Sosnovskikh, V.Y.; Safrygin, A.V.; Anufriev, V.A.; Eltsov, O.S.; Iaroshenko, V.O. *Tetrahedron Lett*. **2011**, 52, 6271.
13. Iaroshenko, V.O.; Abbasi M.S.A.; Villinger, A.; Langer, P. *Tetrahedron Lett*. **2011**, 52, 5910.

14. Mazimba, O.; Masesane I.B.; Majinda R.R. *Tetrahedron Lett.* **2011**, 52, 6716.
15. Samshuddin, S.; Narayana, B.; Sarojini, B.K.; Yathirajan, H.S.; Raghavendra, R. *Der Pharma Chemica* **2012**, 4, 1445.
16. Al-Jaber, N.A.; Bougasim, A.S.A.; Karah, M.M.S. *J. Saudi Chem. Soc*. **2012**, 16, 45.
17. Roman, G. *Acta Chim. Slov*. **2004**, 51, 537.
18. Rao, H.S.P.; Jothilingam, S. *J. Chem. Sci.* **2005**, 117, 323.
19. Raghuvanshi, R.S.; Singh, K.N. *Indian J. Chem*. **2009**, 48B, 1161.
20. Mayekar, A.N.; Li, H.; Yathirajan, H.S.; Narayana, B.; Kumari, N.S. *Int. J. Chem*. **2010**, 2, 114.
21. Krasovsky, A.L.; Nenajdenko, V.G.; Balenkova, E.S. *Tetrahedron* **2001**, 57, 201.