Accepted Manuscript

Synthesis of aurones under neutral conditions using a deep eutectic solvent

Ian Hawkins, Scott T. Handy

PII: S0040-4020(13)01347-1

DOI: 10.1016/j.tet.2013.08.060

Reference: TET 24749

To appear in: *Tetrahedron*

Received Date: 5 July 2013

Revised Date: 20 August 2013

Accepted Date: 21 August 2013

Please cite this article as: Hawkins I, Handy ST, Synthesis of aurones under neutral conditions using a deep eutectic solvent, *Tetrahedron* (2013), doi: 10.1016/j.tet.2013.08.060.

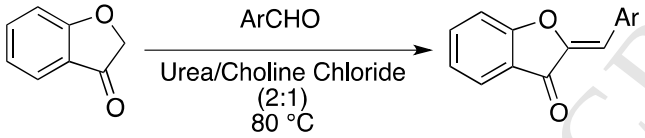
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis of aurones under neutral conditions using a deep eutectic solvent

Leave this area blank for abstract info.

Ian Hawkins and Scott T. Handy
Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37132



Tetrahedron
journal homepage: www.elsevier.com

Synthesis of aurones under neutral conditions using a deep eutectic solvent

Ian Hawkins and Scott T. Handy*

Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37132

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
condensation
green chemistry
ionic liquid
auronrs
choline chloride

ABSTRACT

Aurones are an interesting, but little studied member of the flavanoid family of natural products. Of the various methods available for their synthesis, the simplest involves the condensation of a coumaranone with an aldehyde. This reaction can be performed under acidic or basic conditions. We have recently discovered an effectively neutral set of conditions that employ the deep eutectic solvent comprised of choline chloride and urea as both solvent and catalyst. Modest to good yields can be achieved for a range of aldehydes, thereby facilitating further study of aurones from both a biological as well as a spectroscopic perspective.

* Corresponding author. Tel.: +0-615-217-3271; fax: +0-615-898-5182; e-mail: shandy@mtsu.edu

1. Introduction

1.1. Aurones

Aurones are a family of natural compounds that are found in plants and are part of a larger family of natural products known as flavonoids.[1-3] This family consists of flavones, isoflavones, chalcones, and aurones and are mainly secondary metabolites of plants found in fruits and flowers. (Fig. 1) Aurones in particular have been found to be involved in the coloring of fruits and flowers.[4] While flavones and chalcones have been well studied over the years for various therapeutic effects, aurones have not been as well studied. In early studies, aurones have been found to be possibly beneficial in anti-cancer therapies,[5] in the treatment of malaria,[6] and in microbial infections.[7] Aurones have shown higher activities in these assays when compared with the corresponding flavones and chalcones. These early studies show promise in the use of aurones in many different medical applications.[2,3]

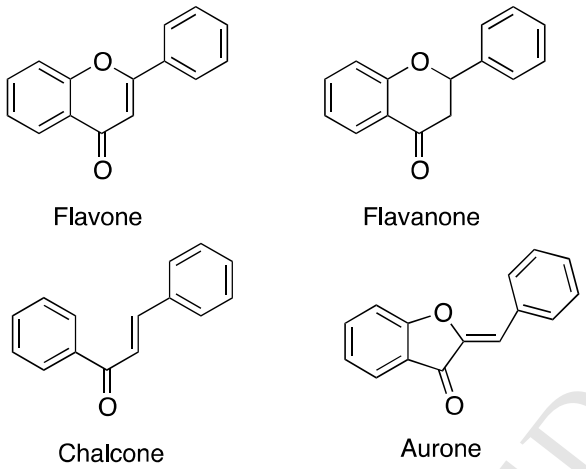
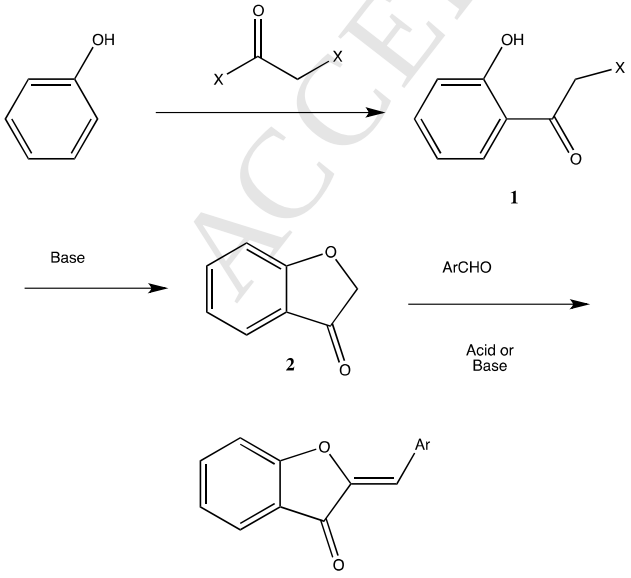


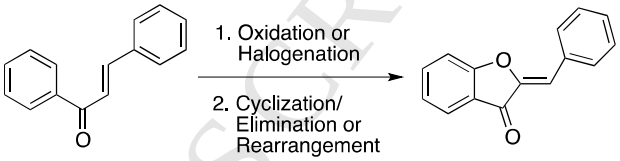
Figure 1. Some Flavonoid Sub-classes

Aurones are synthesized in plants by oxidation, cyclization, and rearrangement of chalcones by an enzyme called aureusidin synthase.[8,9,10] In the lab, however, several methods have been employed. One of the older methods involves the condensation of an aldehyde with a coumaranone. The coumaranone fragment in turn can be formed several ways, including Friedel-Crafts acylation of phenol derivatives.[11] The compound is then hydrolyzed to ketone **1** and then cyclization takes place forming the coumaranone derivative **2**. (Scheme 1)



Scheme 1. Coumaranone Synthesis

An alternate approach is based upon the biosynthetic pathway and follows the same procedure of oxidation followed by cyclization of the aurone.[12,13] (Scheme 2) Chalcones can also be brominated first and then cyclization occurs in a KOH/EtOH solvent.[14] Also the use of thallium (III) nitrate in oxidative rearrangement of chalcones[15] and the use of gold catalyzed cyclization of 2-(1-hydroxyprop-2-ynyl)phenols have been reported recently.[16]



Scheme 2. Biosynthetic Pathway

Returning to the condensation approach, the reaction between coumaranone and an aldehyde involves the use of acid or base catalyzed conditions. Among the many possible variations, one of the milder is the use of neutral alumina to mediate the condensation.[12] Here we report the acid- and base-free synthesis of aurones by the condensation of coumaranone with arylaldehydes using the deep eutectic solvent of choline chloride and urea.

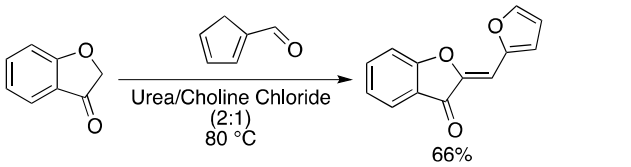
1.2. Deep Eutectics

Deep eutectic solvents are solvents composed of two or more materials where the melting point is drastically reduced compared to that of the original two components.[17] The choline chloride/urea (CC/U) deep eutectic solvent is quite interesting and has been more extensively studied for several reasons. First, the two components are inexpensive, readily available in large quantities, and non-toxic. Further, it can be seen as a much less expensive alternative to room temperature ionic liquids. To date, deep eutectic solvents have been most extensively explored in areas such as metal extraction and electroplating.[18] The use of a mixture of choline chloride and urea forms a very inexpensive solvent and a wide range of solutes have high solubilities in this mixture. Abbott et. al. have looked specifically at choline chloride and urea mixtures and determined that it is one of the few deep eutectic solvents that have freezing points below ambient temperatures.[19,20] This makes it a useful solvent for ambient temperature reactions. Abbott et. al. also established that a molar ratio of urea to choline chloride of 2:1 results in the optimal eutectic with a freezing point of 12°C. Despite their promising attributes, deep eutectic solvents remain largely unexplored as reaction solvents in Organic synthesis.[21, 17]

2. Results and Discussion

Intrigued by the potential to employ the choline chloride/urea deep eutectic as a solvent in Organic synthesis, we explored a number of simple condensation reactions, including that of coumaranone with aldehydes. (Table 1) Gratifiyingly, the reaction proceeded cleanly in a relatively short time to afford the anticipated aurone products. Neither any additional acid or base was required, so the reactions proceed under effectively neutral conditions. The mild nature of these reaction conditions could

certainly be of use in synthesizing aurones with more sensitive functionality such as the furan-containing aurone (Scheme 3). When this reaction was attempted using even the mild neutral alumina conditions of Varma, a very low 16% yield of the aurone was formed, while in CC/U a modest 66% yield was isolated, with no need for chromatography. In addition, the simplicity of the reaction conditions renders the method quite user friendly: simply mixing the coumaranone, and aryl aldehydes in the urea/choline chloride solvent overnight at 80°C followed by an extractive work-up affords the desired products. This reaction is easily accomplished for most of the aryl aldehydes overnight and because the coumaranone is heat labile the aldehyde is the only other material potentially remaining. Product isolation can be readily accomplished by simple partitioning between methylene chloride and water. Most of the reactions required no further purification. This procedure makes it easy to make numerous aurones in a short amount of time with little effort. The choline chloride/urea solvent is inexpensive and presents a wonderful alternative to standard ionic liquid catalyzed reactions. This condensation reaction displays the possible future utility of deep eutectic solvents as catalysts and solvents.

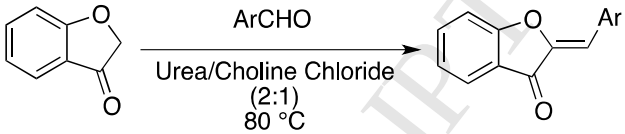


Scheme 3. Furan Aurone Syntheses.

In principle, the aurone products could form as E or Z isomers. In practice, all existing reports note that the product is mostly, or exclusively formed as the thermodynamically more stable Z isomer. That has been our assumption in the present work and is supported by comparison of melting point and spectroscopic data for those aurones previously reported in the literature. Spectroscopic trends further support this assignment as analysis of ^{13}C NMR data for aurones by Pelter and co-workers has noted that the Z isomer of aurones affords an olefinic signal around 111 ppm, while the E isomer affords an olefinic signal roughly 9-10 ppm higher.[22] In all cases, our spectra have signals in the 110 ppm region.

It is also worth noting that there were issues with purification. Crude yields following extraction of the aurone from the DES were all near quantitative, but in some cases contained unreacted aldehyde. Purification via chromatography was not satisfactory as the recovery was quite poor. Fortunately, simple trituration or recrystallization from methanol was sufficient to afford pure samples of the desired products.

One hypothesis of how this DES promotes the reaction is via hydrogen-bonding activation of the aldehyde. Support of this hypothesis comes from a test reaction in an alternative deep eutectic solvent: choline chloride/glycerol. Under the same reaction conditions (time and temperature), a much slower reaction occurs, affording roughly 40% conversion of the *p*-anisaldehyde to the aurone product after 12 hours (compared to 96% in choline chloride/urea). For this reason, we propose that the choline chloride/urea deep eutectic solvent catalyzes the reaction via hydrogen-bonding activation of the aldehyde. Urea is known to be a weak organocatalyst, with its activity largely diminished due to intermolecular hydrogen-bonding.[23] Still, the very high concentrations of urea present in the deep eutectic can likely overcome this weakness and result in effective catalysis. The stronger hydrogen-bonding capabilities and preorganized nature of urea compared to glycerol account for the difference in activity of the two deep eutectic solvents observed in this study. Further applications and confirmation of this hypothesis are underway and will be reported in due course.



Entry	Ar	Yield (time)
1	2,3,4-Trimethoxybenzaldehyde	68% (12 h)
2	3,4,5-Trimethoxybenzaldehyde	73% (48 h)
3	3,4-Dimethoxybenzaldehyde	66% (12 h)
4	3-Nitrobenzaldehyde	40% (12 h)
5	4-Nitrobenzaldehyde	59% (48 h)
6	4-Cyanobenzaldehyde	67% (12 h)
7	4-Bromobenzaldehyde	58% (48 h)
8	Thiophene-2-carboxaldehyde	66% (12 h)
9	Pyrrole-2-carboxaldehyde	60% (12 h)
10	Pyridine-4-carboxaldehyde	54% (36 h)
11	4-Phenylbenzaldehyde	61% (12 h)
12	trans-Cinnamaldehyde	78% (12 h)
13	2-Furyl	66% (12 hr)

Table 1. Aurone Synthesis Results

3. Conclusion

Aurones are an interesting, but little studied member of the flavanoid family of natural products. Of the various methods available for their synthesis, the simplest involves the condensation of a coumaranone with an aldehyde. This reaction can be performed under acidic or basic conditions. We have recently discovered an effectively neutral set of conditions that employ the deep eutectic solvent comprised of choline chloride and urea as both solvent and catalyst. Modest to good yields can be achieved for a range of aldehydes, thereby facilitating further study of aurones from both a biological as well as a spectroscopic perspective. The results of these studies will be reported in due course.

4. Experimental section

4.1. General

All ^1H NMR spectra were collected using a JEOL 500 MHz spectrometer, and the chemical shifts are reported in δ (ppm) relative to TMS. ^{13}C NMR spectra were also collected using a JEOL 500 MHz spectrometer and are reported in δ (ppm) relative

to the $CHCl_3$ signal. Infrared spectra were taken neat using a Varian 800 FT-IR with a Pike MIRacle ATR. Microwave reactions were performed using a CEM Discover microwave reactor. All solid products were recrystallized from methanol.

4.2. General procedure for generation of Choline Chloride/Urea solvent

Choline chloride (7 g, 0.050 mol) and urea (6 g, 0.10 mol) were combined in a vial and heated with shaking overnight at 80 °C on a JKEM orbital shaker at 150 rpm.

4.3. General procedure for Condensation of Coumaranone and aryl aldehydes

To coumaranone (1mmol) was added the aryl aldehyde (1mmol) and 2 mL of Choline Chloride/Urea solvent in a 5 mL sealed vial. The reaction was stirred at 80 °C for the specified time (Table 1). The reaction mixture was then diluted with water (10 mL) and extracted with methylene chloride (3 x 10 mL). The organic layer was then concentrated *in* vacuo to afford the product. In most cases, this product was spectroscopically pure, except where noted.

4.4. (Z)-2-(2,3,4-trimethoxybenzylidene)benzofuran-3(2H)-one (Table 1, entry 1)[23]

mp = 115-120 °C. IR ν=1702, 1645, 1589, 1496, 1464, 1285, 1204, 1191, 1131, 1092, 1008, 910, 885, 802, 759, 732, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ= 3.86 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 6.77 (d, *J*=9.15 Hz , 1H), 7.17 (t, *J*=7.45 Hz, 1H), 7.24-7.28 (m, 2H), 7.58 (t, *J*=1.15 Hz 1H), 7.77 (d, *J*=6.3 Hz, 1H), 8.06 (d, *J*=8.6 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=56.13, 60.96, 61.96, 107.61, 112.86, 119.21, 121.92, 123.31, 124.63, 127.37, 136.52, 142.27, 146.61, 153.92, 155.62, 165.57, 184.38. HRMS: M^+, found 312.32203. $C_{18}H_{14}O_5$ requires 312.32204.

4.5. (Z)-2-(3,4,5-trimethoxybenzylidene)benzofuran-3(2H)-one (Table 1, entry 2)[24]

The crude solid product required further purification on a silica column with 50% CH_2Cl_2/Hexanes followed by a wash with 10% EtOAc/Hexanes. mp = 175-178 °C. IR ν=1708, 1647, 1602, 1581, 1505, 1460, 1336, 1296, 1244, 1189, 1151, 1125, 1098, 1005, 879, 758, 668, 640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=6.74 (s, 1H), 7.10 (s, 2H), 7.15 (t, J=7.45 Hz, 1H), 7.23 (d, J=8 Hz, 1H), 7.57 (t, J=6.9 Hz, 1H), 7.73 (d, J=6.85 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=56.15 (2C), 60.97, 108.85 (2C), 112.82, 113.30, 121.65, 123.48, 124.63, 127.62, 136.71, 140.08, 146.34, 153.27 (2C), 165.84, 184.48. HRMS: M^+, found 312.32207. $C_{18}H_{14}O_5$ requires 312.32204.

4.6. (Z)-2-(3,4-dimethoxybenzylidene)benzofuran-3(2H)-one (Table 1, entry 3)[25]

mp = 123-130 °C. IR ν=1705, 1595, 1522, 1463, 1296, 1269, 1248, 1202, 1153, 1124, 1019, 885, 758, 731, 645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ= 3.86 (s, 3H), 3.89 (s, 3H), 6.78 (s, 1H), 6.86 (d, J=8.6 Hz, 1H), 7.13 (t, J=7.4 Hz, 1H), 7.23 (d, J=8.6 Hz, 1H), 7.41 (d, J=10.3 Hz, 1H), 7.45 (d, J=1.7 Hz, 1H), 7.56 (t, J=8.55 Hz, 1H), 7.72 (d, J=7.45 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=111.13, 112.79, 113.67 (2C), 121.81, 123.30, 124.54, 125.20, 125.98, 136.51, 145.86, 148.98, 150.82, 165.70, 184.43. HRMS: M^+, found 282.29574. $C_{17}H_{14}O_4$ requires 282.29576.

4.7. (Z)-2-(3-nitrobenzylidene)benzofuran-3(2H)-one (Table 1, entry 4)[26]

mp = 163-166 °C. IR ν= 1708, 1655, 1601, 1531, 1475, 1458, 1347, 1303, 1191, 1132, 1098, 885, 810, 757, 734, 699, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ= 6.86 (s, 1H), 7.25 (t, J=7.75 Hz, 1H), 7.38 (d, J=8 Hz, 1H), 7.62 (t, J=8 Hz, 1H), 7.69 (t, J=8.55 Hz, 1H), 7.80 (d, J=8.6 Hz, 1H), 8.13 (d, J=7.45 Hz, 1H), 8.22 (d, J=8 Hz, 1H), 8.79 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=109.62, 113.11, 121.07, 123.95, 124.04, 124.88, 125.52, 129.79, 133.91, 136.71, 137.55, 147.86, 148.59, 166.23, 184.52. HRMS: M^+, found 267.24077. $C_{15}H_9NO_4$ requires 267.2408.

4.8. (Z)-2-(4-nitrobenzylidene) benzofuran-3(2H)-one (Table 1, entry 5)[27]

The crude solid product required further purification on silica column with 50% CH_2Cl_2/Hexanes. mp = 165-170 °C. IR ν=1711, 1603, 1517, 1476, 1458, 1343, 1322, 1299, 1204, 1188, 1130, 1111, 1097, 1033, 889, 860, 760, 688, 647 cm^{-1}; ^{11}H NMR (500 MHz, $CDCl_3$): δ=6.85 (s, 1H), 7.26 (t, J=7.45Hz, 1H), 7.35 (d, J=8.05Hz, 1H), 7.69 (t, J=8.65 Hz, 1H), 7.82 (d, J=6.85 Hz, 1H), 8.04 (d, J=9.15 Hz, 2H), 8.28 (d, J=8.6 Hz, 2H); ^3C NMR (500 MHz, $CDCl_3$): δ=109.35, 113.01, 102.97, 123.85 (2C), 124.22, 125.06, 131.61 (2C), 137.29, 138.60, 148.37, 166.30, 184.94, 206.98. HRMS: M^+, found 267.2408. $C_{15}H_9NO_4$ requires 267.2408.

4.9. (Z)-4-((3-oxobenzofuran-2(3H)-ylidene)methyl)benzonitrile (Table 1, entry 6)[27]

mp = 181-184 °C. IR ν= 1703, 1650, 1602, 1475, 1461, 1302, 1190, 1130, 1108, 885, 833, 755, 734, 699, 664, 645, 626 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=6.79 (s, 1H), 7.24 (t, J=6.85 Hz, 1H), 7.32 (d, J=8.6 Hz, 1H), 7.65-7.70 (m, 3H), 7.79 (d, J=7.45, 1H), 7.97 (d, J=8.55 Hz, 2H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=110.09, 112.65, 113.10, 118.65, 121.20, 124.17, 125.04, 131.61 (2H), 132.56 (2H), 136.83, 137.64, 148.21, 166.34, 184.65. HRMS: M^+, found 247.25303. $C_{16}H_9NO_2$ requires 247.25300.

4.10. (Z)-2-(4-bromobenzylidene)benzofuran-3(2H)-one (Table 1, entry 7)[28]

The crude solid product required further purification on silica column with 50% CH_2Cl_2/Hexanes. mp = 152-158 °C. IR ν= 1714, 1655, 1601, 1487, 1474, 1460, 1298, 1205, 1186, 1128, 1112, 1099, 1071, 1008, 884, 821, 756, 697, 653, 626 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=6.81 (s, 1H), 7.24 (t, J=7.45 Hz, 1H), 7.34 (d, J=8 Hz, 1H), 7.58 (d, J=8.6 Hz, 2H), 7.67 (t, J=8.6 Hz, 1H), 7.78 (d, J=8.6 Hz, 2H), 7.81 (d, J=8.6 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=111.47, 112.87, 121.39, 123.57, 124.21, 124.66, 131.03, 132.07 (2C), 132.61 (2C), 136.99, 146.99, 165.99, 184.58. HRMS: M^+, found 300.15356. $C_{15}H_9BrO_2$ requires 300.15359.

4.11. (E)-2-(thiophen-2-ylmethylene)benzofuran-3(2H)-one (Table 1, entry 8)[29]

mp = 92-96 °C. IR ν=1698, 1684, 1645, 1593, 1504, 1475, 1458, 1417, 1391, 1328, 1295, 1232. 1185, 1124, 1095, 992, 881, 846, 756, 710, 695, 625 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.17 (t, J=4cHz, 1H), 7.20 (s, 1H), 7.24 (t, J=7.45cHz, 1H), 7.27 (s, 1H), 7.36 (d, J=8.55 Hz, 1H), 7.57 (d, J=3.45 Hz, 1H), 7.63 (d, J=5.15Hz, 1H), 7.66 (t, J=8.55Hz, 1H), 7.81 (d, J=7.45Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=107.12, 112.92, 122.25, 123.52, 124.58, 128.09, 131.54, 133.17, 135.55, 136.71, 145.33, 165.65, 183.85. HRMS: M^+, found 228.27134. $C_{13}H_8SO_2$ requires 228.27132.

4.12. (Z)-2-((1H-pyrrol-2-yl)methylene)benzofuran-3(2H)-one (Table 1, entry 9)

mp = 138-142 °C. IR ν=1687, 1635, 1594, 1477, 1458, 1430, 1319, 1300, 1195, 1143, 1125, 1100, 1039, 885, 868, 819, 756, 725, 696 cm-^{1}; ^1H NMR (500 MHz, $CDCl_3$): δ= 6.72 (s, 1H),

6.96 (s, 1H), 7.03 (s, 1H), 7.14 (s, 1H), 7.19-7.23 (m, 1H), 7.30 (d, J=8 Hz, 1H), 7.60-7.63 (m, 1H), 7.79 (d, J=1.15 Hz, 1H), 9.56 (bs, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=105.16, 111.43, 112.58, 118.43, 122.62, 123.37, 124.23, 124.61, 126.10, 136.00, 143.70, 164.53, 183.00. HRMS: M^+, found 211.22002. $C_{13}H_9NO_2$ requires 211.22000.

4.13. (Z)-2-(pyridine-4-ylmethylene)benzofuran-3(2H)-one (Table 1, entry 10)[30]

mp = 89-93 °C. IR ν= 1647, 1599, 1474, 1464, 1416, 1378, 1300, 1201, 1130, 828, 756, 734, 697, 675, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=6.87 (s, 1H), 7.43 (t, J=7.45 Hz, 2H), 7.57 (d, J=8.6 Hz, 1H), 7.71 (d, J=7.45 Hz, 1H), 7.75 (d, J=5.75 Hz, 2H), 8.20 (d, J=6.3 Hz, 1H), 8.79 (d, J=6.3 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=109.34, 118.24, 119.86 (2C), 124.07, 124.73, 125.86, 134.43, 150.78 (2C), 156.20, 160.59, 178.22. HRMS: M^+, found 223.23100. $C_{14}H_9NO_2$ requires 223.23100.

4.14. (Z)-2-(biphenyl-4-ylmethylene)benzofuran-3(2H)-one (Table 1, entry 11)[31]

mp = 63-68 °C. IR *ν*=1702, 1646, 1597, 1486, 1461, 1299, 1209, 1185, 1150, 1128, 1109, 1007, 886, 838, 755, 729, 696 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$): δ= 6.95 (s, 1H), 7.24 (t, J=7.45 Hz, 2H), 7.35-7.71 (m, 8H), 7.82 (d, J=8.55 Hz, 1H), 8.01 (d, J=8.05 Hz, 2H). ^{13}C NMR (500MHz, $CDCl_3$): δ=112.84, 112.96, 121.67, 123.50, 124.70, 127.08, 127.36, 127.40, 127.52, 127.92, 128.26, 128.77, 128.93, 131.28, 132.04, 136.90, 140.08, 142.52, 146.94, 166.08, 184.75. HRMS: M^+, found 298.34095. $C_{21}H_{14}O_2$ requires 298.34096.

4.15. (Z)-2-((E)-3-phenylallylidene)benzofuran-3(2H)-one (Table 1, entry 12)

mp = 57-64 °C. IR ν=1699, 1638, 1608, 1475, 1462, 1298, 1198, 1149, 1117, 970, 879, 753, 698, 669 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$): δ=6.78 (d, J=11.45 Hz, 1H) 7.02 (d, J=16.05 Hz, 1H), 7.18 (t, J=7.45 Hz, 1H), 7.24-7.38 (m, 6H), 7.54 (d, J=7.45 Hz, 1H), 7.62 (t, J=8.6 Hz, 1H), 7.76 (d, J=7.45 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=112.58, 114.44, 120.79, 122.42, 123.34, 124.62, 127.55 (2H), 128.98 (2H), 129.46, 136.39, 136.80, 141.52, 147.46, 165.52, 183.91. HRMS: M^+, found 248.28106. $C_{17}H_{12}O_2$ requires 248.28108.

4.16. (Z)-2-(furylmethylene)benzofuran-3(2H)-one (Table 1, entry 13)

mp = 66-68 °C. IR ν=1730, 1650, 1610, 1480, 1300, 1190, 1105, 850, 760 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$): δ=6.56 (br s, 1H) 6.85 (s, 1H), 7.10 (d, J=3.45 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.61-7.57 (m, 2H), 7.75 (d, J=8.6 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ=101.57, 112.81, 113.11, 117.24, 121.87, 123.39, 124.41, 136.62, 144.87, 145.34, 148.65, 165.59, 183.90. HRMS: M^+, found 196.05241. $C_{13}H_8O_2$ requires 196.05243

5. References and notes

1. Boumendjel, A. *Cur. Med. Chem.* **2003,** *10*, 2621-2630.
2. Haudecoeur, R.; Boumendjel, A. *Cur. Med. Chem.* **2012**, 19, 2861-2875.
3. Zwergel, C.; Gaascht, F.; Valente, S.; Diedrich, M.; Bagrel, D.; Kirsch, G. *Nat. Prod. Commun.* **2012**, 7, 389-394.
4. Harborne, J.B.; Williams, C.A. *Phytochem.* **2000**, 55, 481-504.
5. Lawrence, N.J.; Rennison, D.; McGowan, A.T.; Hadfield, J.A. *Bioorg. & Med. Chem. Let.* **2003,**13, 3759-3763.
6. Kayser, O.; Kiderlen, A.F.; Brun, R. *Planta Medica.* **2001**, 67, 718-721.
7. Bandgar, B.P.; Patil, S.A.; Korbad, B.L.; Biradar, S.C.; Nile, S.N.; Khobragade, C.N. *Euro. J. of Med. Chem.* **2010**, 45, 3223-3227.
8. Nakayama, T.; Sato, T.; Fukui, Y.; Yonekura-Sakakibara, K.; Hayashi, H.; Tanaka, Y.; Kusumi, T.; Nishino, T. *FEBS Lett.*, **2001**, 499, 107-111.
9. Nakayama, T.; Yonekura-Sakakibara, K.; Sato, T.; Kikuchi, S.; Fukui, Y.; Fukuchi-Mizutani, M.; Ueda, T.; Nakao, M.; Tanaka, Y.; Kusumi, T.; Nishino, T. *Science.* **2000**, 290, 1163-1166.
10. Nakayama, T. *J Biosci and Bioengineering* **2002**, *94*, 487-491.
11. Adams, C.J.; Main, L. *Tetrahedron*. **1992**, 48, 9929-9938.
12. Varma, R.S.; Varma, M. *Tetrahedron Lett.* **1992**, 33, 5937-5940.
13. Donnelly, D.J.; Donnelly, J.A.; Keegan, J.R. *Tetrahedron*, **1977**, 33, 3285-3288.
14. Bose, G.; Modal, E.; Khan, A.T.; Bordoloi, M.J. *Tetrahedron Lett.* **2001**, 42, 8907-8909.
15. Thakkar, K.; Cushman, M. *Tetrahedron Lett.* **1994**, 35, 6441-6444.
16. Harkat, H.; Blanc, A.; Weibel, J.; Pale, P. *J. Org. Chem.* **2008**, 73, 1620-1623.
17. Russ, C.; Koenig, B. *Green Chem.* **2012**, *14*, 2969-2982.
18. Abbott, A.P.; Frisch, G.; Hartley, J.; Ryder, K.S. *Green Chem.* **2011**, *13*, 471-481. Zhang, Q.; Vigier, K. D. O.; Royer, S.; Jerome, F. *Chem. Soc. Rev.* **2012**, *41*, 7108-7146. Francisco, M.; van den Bruinhorst, A.; Kroon, M.C. *Angew. Chem. Int. Ed.* **2013**, *52*, 3074-3085
19. Abbott, A.P.; Capper, G.; Davies, D.L.; Rasheed, R.K.; Tambyrajah, V. *Chem. Commun.* **2003**, 70-71.
20. Abbott, A.P.; Boothby, D.; Capper, G.; Davies, D.L.; Rasheed, R.K. *J. Am. Chem. Soc.* **2004**, 126, 9142-9147.
21. Singh, B.; Lobo, H.; Shankarling, G. *Cat. Lett.* **2011**, *141*, 178-182. Pawar, P.M.; Jarag, K.J.; Shankarling, G.S. *Green Chem.* **2011**, *13*, 2130-2134. Phadtare, S.B.; Shankarling, G.S. *Green Chem.* **2010**, *12*, 458-462.
22. Pelter, A.; Ward, R.S.; Heller, RH.G. *J. Chem. Soc. Perkin Trans.1* **1979**, 328-329.
23. Schreiner, P.R. *Chem. Soc. Rev.* **2003**, *32*, 289-296.
24. Imafuku, K.; Honda, M.; Mcomie, J.F.W. *Synthesis* **1987**, 199-201.
25. Morimoto, M.; Fukumoto, H.; Toki, H.A.; Komai, K. *J. Ag. & Food Chem.* **2007**, *55*, 700-705.
26. Detsi, A.; Majdalani, M.; Kontogiorgis, C.A.; Hajipavlou-Litina, D.; Kefalas, P. *Bioorg.& Med. Chem.* **2009**, *17*, 8073-8085.
27. Donnelly, J.A.; Emersosns, G.M. *Tetrahedron* **1990**, *46*, 7227-7236.
28. Paronav, T.; Bognar, R.; Litkei, G. *Tetrahedron* **2984**, *40*, 2555-2562.
29. Manjulatha, K.; Srinivas, S.; Mulakayala, N.; Rambabu, B.D.; Prabhakar, M.;Arunasree, K.M.; Pal, M. *Bioorg. & Med. Chem. Lett.* **2012**, *22*, 6160-6165.
30. Donnelly, D.J.; Donnelly, J.A.; Keegan ,J.R. *Tetrahedron* **1977**, *33*, 3289-3294.
31. Bobbitt, J.M.; Katritzk, A.R.; Kennewel, P.D.; Snarey, M. *J. Chem. Soc.B* **1968**, 550.

Click here to remove instruction text...