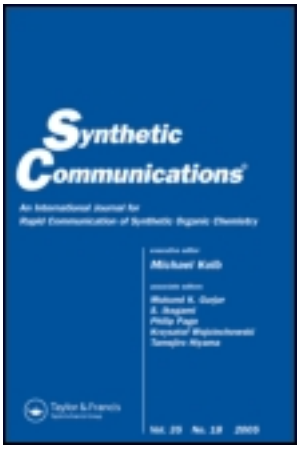

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Route to Highly Functionalized Chalcone-Based Pyranocoumarins via Iodine-Promoted Michael Addition Followed by Cyclization of 4-Hydroxycoumarins

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Accepted author version posted online: 18 Jun 2013.

To cite this article: Naseem Ahmed & B. Venkata Babu (2013) Efficient Route to Highly Functionalized Chalcone-Based Pyranocoumarins via Iodine-Promoted Michael Addition Followed by Cyclization of 4-Hydroxycoumarins, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:22, 3044-3053, DOI: 10.1080/00397911.2012.763099

To link to this article: http://dx.doi.org/10.1080/00397911.2012.763099

Synthetic Communications®, 43: 3044–3053, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.763099

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EFFICIENT ROUTE TO HIGHLY FUNCTIONALIZED CHALCONE-BASED PYRANOCOUMARINS VIA IODINE-PROMOTED MICHAEL ADDITION FOLLOWED BY CYCLIZATION OF 4-HYDROXYCOUMARINS

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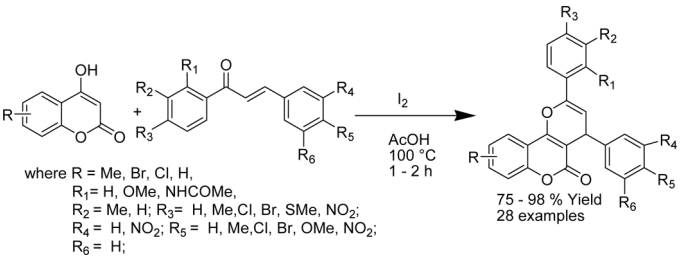
GRAPHICAL ABSTRACT



Abstract *Molecular iodine is used as an efficient promoter in the regioselective synthesis of highly functionalized chalcone-based pyranocoumarin derivatives using 4-hydroxycoumarin in acetic acid solvent at 100 °C. Under optimized reaction conditions, our protocol (Michael addition followed by intermolecular cyclization) has tolerance for many functional groups and gave products in good to excellent yields (75–98%) within 1–2 h.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource: Full experimental and spectral details.]*

Keywords Annulation reaction; chalcones-based pyranocoumarins; 4-hydroxycoumarin; Michael addition; molecular-iodine promoter

INTRODUCTION

Functionalized pyranocoumarins are an important class of oxygen-containing heterocyclics. They have shown various biological and pharmaceutical applications[1–3] such as antipsoriasis,[1a] anti–mycobacterium tuberculosis,[2a] anti-inflammatory, antiviral hepatitis,[2b] anticytotoxic,[2b] antifungal,[2c] anticoagulant, insecticidal, anticancer,[3a] antibacterial,[3b] antitumor,[3d] anti-HIV,[3e] and antiproliferative[3g]

Received October 10, 2012.
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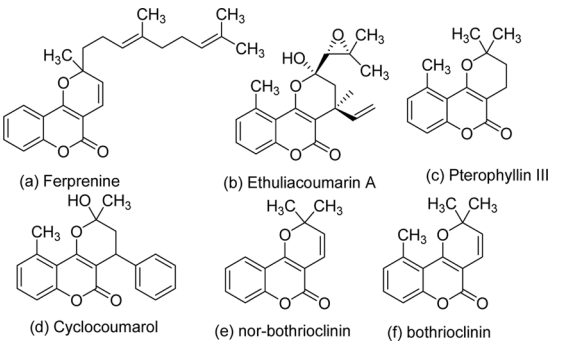


Figure 1. Biologically active pyranocoumarin derivatives.

applications. Many pyranocoumarins are natural products and widely distributed in higher plants such as *Calophyllumlanigerium*, *Calophyllumteysmannii*, *Zanthoxylumchiloperone*, and Meliaceae trees. These natural products are used as versatile motifs in the synthesis of useful organic compounds as well as natural products and semisynthetic derivatives of natural products for better pharmaceutical,[4a] medicinal,[4b] and photochromic[4c] properties. They are found as core structures in many natural products such as ferprenine,[5a] ethuliacoumarin A,[5b] pterophyllin-III,[5c] cyclocoumarol,[5d] and norbothrioclinin, and bothrioclinin.[5f] These natural products were found to be potent anticoaglent, anti-HIV, and antiproliferative agents (Fig. 1).

Generally, synthesis of functionalized pyranocoumarin derivatives is difficult. Therefore, development of facile and convenient methods for synthesis has attracted great attention from synthetic chemists because of biological importance. During pyranocoumarin synthesis, typically C–C bond formation followed by cyclization takes place, where chemists face problems in selecting efficient catalyst for regioselective products, unavailable precursors, expensive and toxic reagents, poor yield, and longer reaction time. Recently, Palmisano et al. synthesized regioselective pyranocoumarin derivatives via hetero-Diels–Alder reaction (HDA). This method failed to synthesize pyranocoumarins because of lack of starting materials such as diene and dienophile derivatives.[5e] Similarly, Lin et al. reported pyranocoumarin synthesis with an I_2-H_2SO_4 system[6] and Berger and Haak used a ruthenium complex system.[7] However, both protocols have drawbacks as moderate yield and poor selectivity in the product. Lin et al. further reported a modified method using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)–mediated oxidative cross-coupling reaction, but it yielded poor regioselectivity.[8] Zhiwei et al.[9] and Moreau et al.[10] reported regioselective synthesis of pyranocoumarins using 4-hydroxycoumarins and α, β-unsaturated aldehydes, but the catalyst is commercially unavailable. Similarly, other methods are also available for the synthesis of pyranocoumarins using 4-hydroxycoumarins and α, β-unsaturated aldehydes[11] and ketones.[12] However, the selectivity and toxicity of the reagents are major problems. Majumdar et al.[13] prepared dihydropyranocoumarin derivatives from 4-prop-2-ynyloxy coumarin via a thiol-mediated radical reaction in a regioselective manner where reactants are commercially not available. Yunkui et al.[14] also synthesized functionalized pyranocoumarins in a selective approach using a gold(III) catalyst along with silver triflate.

In this protocol, drawbacks such as expensive catalyst, poor yield, and poor regioselectivity have been observed.[15] Further, Sarma et al. prepared pyranocoumarins using cerium(IV) ammonium nitrate (CAN)–mediated oxidative addition of 4-hydroxycoumarin to 2-methyl-3-buten-2-ol, which gave good selectivity of Michael addition but poor yield during pyran ring formation.[15b] Therefore, there is still a need to develop efficient and selective reaction protocols with broader substrate scope in the synthesis of functionalized pyranocoumarins.

Molecular iodine has received considerable attention as an inexpensive, less toxic, environmentally compatible, selective, cheap, and readily available catalyst in various organic transformations because of its moderate Lewis acidity and water tolerance.[16] However, the catalytic action has not been completely investigated from a mechanistic point of view[17] and compatibility with many substrates is undetermined. In recent papers,[18] iodine was proposed as a very efficient catalyst in the Mukaiyamaaldol reaction of 2-(trimethylsilyloxy)furan with aromatic and aliphatic aldehydes, selective and efficient conjugate additions of pyrrole to nitro-olefins, or α, β-unsaturated ketones, novel multicomponent reactions (MCRs), and domino reaction strategy for heterocyclic synthesis; *meso*-substituted porphyrins synthesis;[19] air-mediated tandem condensation; imino-Diels–Adler; isomerization; oxidation of simple and readily available amines, aldehydes, alkynes, and disulfidation reactions; protection of carbonyl and hydroxyl groups; oxidation of benzylic alcohols; cycloaddition; and aromatization of α, β-unsaturated ketones.[19b]

Based on these advantages of iodine as a catalyst/promoter and our interest in Lewis acid catalysis for Michael addition and annulation reactions during heterocycle synthesis,[20] we herein report an efficient and regioselective method for the synthesis of biologically important and highly functionalized pyranocoumarin derivatives using easily available 4-hydroxycoumarins and chalcones in the presence of molecular iodine promoter in acetic acid solvent at 100 °C.

Different chalcones were prepared following literature procedure.[21] Initially, we tried MgO, $SnCl_4$, $SnCl_2 \cdot 2H_2O$, $TaCl_5$, $LaCl_3$, ZnO, CuO, $BiNO_3$, CuO, $LaCl_3$, and $TiCl_4$ as Lewis acid catalysts varying 10–100 mol% in different solvents (tetrahydrofuran [THF], toluene, dimethylosulfoxide (DMSO), dimethylformomide (DMF)) from room temperature to reflux temperature for 30 h. We failed to get the product (footnotes in Table 1). Use of AcOH as a catalyst in these solvents gave 5% product yield (entry 1, Table 1). Then, we tried the reaction in neat acetic acid (used as catalyst and solvent) at room temperature as well as reflux temperature and we got enhanced product yield (12%) at reflux temperature (entry 2, Table 1). However, on adding iodine (2–50 mol%) in the reaction mixture at 100 °C, we got a better yield (up to 60%) (entries 3–8, Table 1). Further, when we increased catalyst loading (100 mol%) at room temperature, we got poor yield (5%) (entry 9, Table 1). However, we serendipitously got an excellent yield (98%) within 30 min at 100 °C (entry 10, Table 1). Further increase in catalyst loading (120–200 mol%) gave no difference in the reaction time or product yield (entry 11, Table 1).

In the optimized reaction conditions, we used 4-hydroxycoumarins such as 6-methyl-4-hydroxycoumarin, 6-bromo-4-hydroxycoumarin, and 6-chloro-4-hydroxycoumarin derivatives[22] (entries 20–28, Table 2); different A-ring substituted chalcones as electron-releasing groups such as methyl and halogens, electron-withdrawing groups such as nitro, B-ring substituted chalcones as 3-position

Table 1. Optimization condition of compound **2**

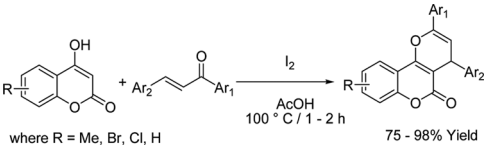
No.	Catalyst	Solvent	Moles (%)	Temperature	Time (h)	Yield (%)
1	AcOH	THF/toluene/ DMSO/DMF	10–20	Reflux	30	5
2	—	AcOH	—	rt–100 °C	30	12
3	I_2	AcOH	2	100 °C	30	10
4	I_2	AcOH	5	100 °C	30	15
5	I_2	AcOH	10	100 °C	30	20
6	I_2	AcOH	25	100 °C	30	32
7	I_2	AcOH	40	100 °C	30	43
8	I_2	AcOH	50	100 °C	30	60
9	I_2	AcOH	100	Rt	30	05
10	**I_2**	**AcOH**	**100**	**100 °C**	**0.5**	**98**
11	I_2	AcOH	120–200	100 °C	0.5	98

Note. MgO, ZnO, CuO, $LaCl_3$, $BiNO_3$, $SnCl_4$, $SnCl_2{\cdot}2H_2O$, $TaCl_5$, $LaCl_3$, $CuBr_2$, and $TiCl_4$: no product obtained.

electron-withdrawing groups; 4-position electron-releasing groups such as methoxy, methyl, dimethyl, and thiomethyl, and poor releasing group such as halides, which furnished the respective products in moderate to excellent yields (75–98%) (Scheme 1, path I). The methoxy group–substituted chalcones gave moderate yield because of inductive effects on Michael addition, and thiophenechalcone and nitro group also gave moderate yield; however, other groups have no substitution effects. In all these cases, entries 1–28 in Table 2, 1,4-Micheal addition followed by annulation reaction (cyclization) and dehydration gave a single product with good regioselectivity and good to excellent yield. However, the reaction of 4-hydroxycoumarins with 2′-hydroxychalcones gave flavanones instead of pyranocoumarins, even prolonging the reaction time (Scheme 1, path III). Here, iodine-promoted reaction in acetic acid at refluxed temperature further enhanced the flavanone formation.[23]In the case of protected 2′-hydroxychalcone, we got the desired product (entry 33, Table 2). Similarly, 2′-aminochalcones gave no product, which might be due to protonation of amino group that forbade the Michael addition reaction (entry 34, Table 2). However, protected 2′-aminochalcones gave the desired product (Scheme 1, path II) (entry 34, Table 2).

All products **1–28** were well characterized by infrared (IR), ^1H and ^{13}C NMR, and mass spectrometry (electrospray ionization) [MS (ESI)] and compared with the literature.[6,15] For example, 4-(4-chlorophenyl)-2-phenylpyrano[3,2-c]chromen-5(4H)-one **(2)** had IR peaks at [ν_{max}(KBr, cm^{-1})] 1720 cm^{-1}, indicating a carbonyl group; and 2979, 2861 cm^{-1}, indicating aromatic C-H stretching. The ^1H NMR ($CDCl_3$, 500 MHz) spectum at δ 5.46 (d, $J = 5.0$ Hz, 1H) showed C-3 proton of pyran ring (Ar-C=C*H*-CH-Ar), and peak at δ 4.59 (d, $J = 5.0$ Hz, 1H) showed C-4 proton of pyran ring (Ar-C=CH-C*H*-Ar). The ^{13}C NMR ($CDCl_3$, 125 MHz) spectrum gave peak at δ 161.2 ppm for the characteristic carbonyl carbon of coumarin ring and 35.09 ppm for C-4 carbon of pyran ring[6,15] (Ar-C=CH-*C*H-Ar), also confirmed by peak in MS-ESI (m/z): $[M^+ + Na]$ of $C_{24}H_{15}ClO_3$: 409.0. Similarly, 2-(3,4-dimethylphe-nyl)-9-methyl-4-phenylpyrano[3,2-c]chromen-5(4H)-one **(26)** had IR peaks at [ν_{max}(KBr, cm^{-1})] 1705 cm^{-1}, indicating a carbonyl group, and

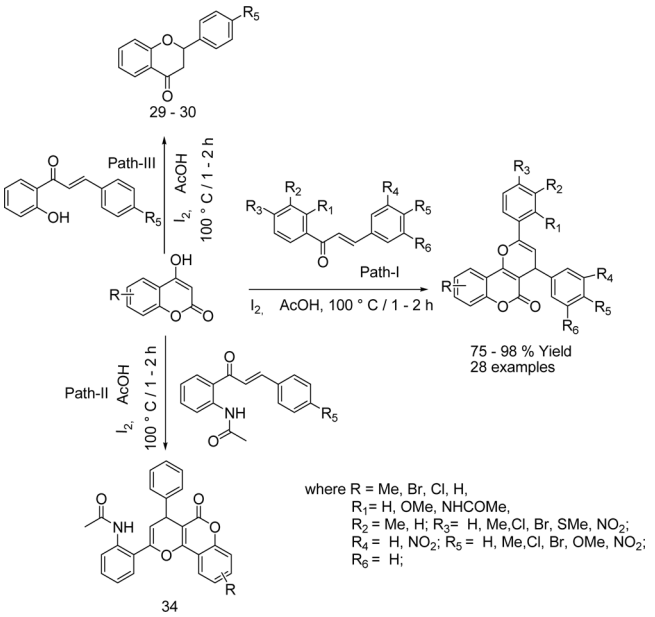
Table 2. Different derivatives of pyranocoumarins



R	Ar_1	Ar_2	Pyrano coumarin	Rxn. time (min)	Yield (%)[a]
H	Ph	Ph	**1**	50	98
H	Ph	4-Cl-Ph	**2**	45	98
H	Ph	4-Br-Ph	**3**	50	96
H	Ph	4-OMe-Ph	**4**	100	90
H	Ph	3-NO_2-Ph	**5**	90	90
H	4-Cl-Ph	Ph	**6**	50	95
H	4-Cl-Ph	4-Br-Ph	**7**	55	94
H	4-Cl-Ph	4-Me-Ph	**8**	100	90
H	4-Cl-Ph	4-OMe-Ph	**9**	100	87
H	4-Br-Ph	Ph	**10**	60	95
H	4-Br-Ph	4-Cl-Ph	**11**	55	96
H	4-Br-Ph	4-Me-Ph	**12**	90	92
H	4-Br-Ph	4-OMe-Ph	**13**	95	89
H	4-NO_2-Ph	4-Me-Ph	**14**	90	90
H	3,4-(di Me)-Ph	Ph	**15**	60	91
H	3,4-(di Me)-Ph	4-Cl-Ph	**16**	70	90
H	3,4-(di Me)-Ph	4-Me-Ph	**17**	75	90
H	3,4-(di Me)-Ph	3-NO_2-Ph	**18**	100	89
H	4-(SMe)-Ph	4-Cl-Ph	**19**	100	87
H	4-(SMe)-Ph	4-Me-Ph	**20**	100	85
Br	Ph	Ph	**21**	50	95
Br	Ph	4-Cl-Ph	**22**	55	95
Br	4-(SMe)-Ph	4-Me-Ph	**23**	95	86
Br	3,4-(di Me)-Ph	4-Cl-Ph	**24**	95	88
Me	Ph	4-Cl-Ph	**25**	60	92
Me	3,4-(di Me)-Ph	Ph	**26**	70	90
Me	4-Cl-Ph	2-Thiophene	**27**	80	80
Cl	Ph	4-Cl-Ph	**28**	70	93
H	2-OH-Ph	Ph	**29**	100	NR[b]
H	2-OH-Ph	4-Br-Ph	**30**	100	NR[b]
H	2-NH_2-Ph	Ph	**31**	100	NR[b]
H	2-NH_2-Ph	4-Cl-Ph	**32**	100	NR[b]
H	2-OMe-Ph	4-Br-Ph	**33**	80	83[a]
H	2-$NHCOCH_3$-Ph	4-Cl-Ph	**34**	100	75[a]

[a]Isolated yield.
[b]No reaction (NR).

2939, 2880 cm^{-1}, indicating aromatic C-H stretching. The ^1H NMR ($CDCl_3$, 500 MHz) spectum at δ 5.68 (d, $J = 5.0$ Hz, 1H) showed a C-3 proton of the pyran ring (Ar-C=C*H*-CH-Ar), a peak at δ 4.60 (d, $J = 5.0$ Hz, 1H) of the C-4 proton of pyran ring (Ar-C=CH-C*H*-Ar), and peaks at δ 2.49 (s, 3H), 2.26 (s, 3H), and 2.20 (s, 3H) of three methyl groups on aromatic rings. The ^{13}C NMR ($CDCl_3$, 125 MHz) gave a peak at δ 161.8 ppm for the characteristic carbonyl carbon of coumarin ring, 36.06 ppm for C-4 carbon of the pyran ring[6,15] (Ar-C=CH-*C*H-Ar), and



Scheme 1. Synthesis of pyranocoumarin derivatives.

peaks at 21.1, 20.0, and 19.7 for three methyl carbons, also confirmed by peaks in ESI-MS (m/z) [$M^{+\cdot}$+Na] of $C_{27}H_{22}O_3$, 417.0. Similarly, other derivatives **1, 3–25**, and **27, 28** were confirmed by their spectral analysis and compared with literature (see the experimental section), and products **29–33** were confirmed by ESI-MS molecular ion peak. Finally, the structure of one of the representative compounds, 2,4-diphenylpyrano[3,2-*c*]chromen-5(4*H*)-one **(1)** was confirmed unambiguously by single-crystal x-ray diffraction analysis (see the supplementary data) (CCDC-895196) (Fig. 2).

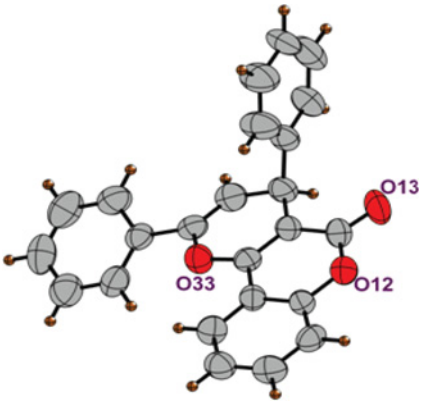
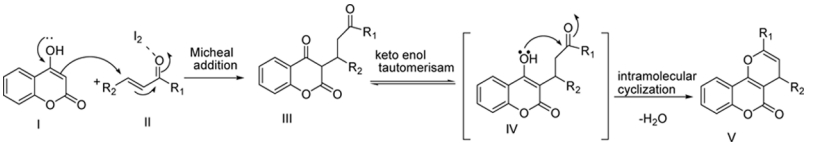


Figure 2. ORTEP diagram of 2,4-diphenylpyrano[3,2-*c*] chromen-5(4*H*)-one (**1a**) (CCDC-895196). (Figure is provided in color online.)



Scheme 2. Plausible mechanism.

A plausible mechanism is proposed in Scheme 2, where molecular iodine ligated with chalcone **(II)** activates Michael addition with 4-hydroxycoumarin **(I)** and forms a 1,5-diketone **(III)** intermediate. The unstable intermediate is equilibrated in keto-enol **(IV)** forms. Further, the intermediate undergoes intramolecular cyclization by the loss of a water molecule to form the desired product **(V)**.

CONCLUSION

In conclusion, we have developed a molecular iodine–promoted efficient and regioselective synthetic method for highly functionalized pyranocoumarin derivatives in good to excellent yield from 4-hydroxycoumarin and chalcone derivatives in AcOH solvent at 100 °C. Our protocol has synthesized functionalized pyranocumarins and has advantages over previous methods such as cheap catalyst, nontoxic and commercially available substrates, economic viability, and environmental compatibility.

EXPERIMENTAL

Commercially available reagents were used without further purification unless mentioned. All reactions were monitored by thin-layer chromatography (TLC) using precoated silica-gel aluminum plates with GF_{254} silica (Spechrochem, Mumbai). Visualization of TLC plates was accomplished with an ultraviolet lamp at 254 nm or in an iodine chamber. Melting points were recorded on a perfit apparatus and are uncorrected. IR spectra of the compounds were expressed as wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. ^1H NMR spectra were recorded in $CDCl_3$ solvent and an internal standard as tetramethylsilane (TMS). Chemical shifts of ^1H NMR spectra were given in parts per million (ppm) and the coupling constant J was measured in hertz. Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet). Mass spectra were recorded by ESI-MS. The x-ray data collection were performed on a Bruker Kappa Apex four circle-CCD diffractometer using graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at 100 K. Images were created in the crystal lattice with Diamond software.

General Procedure: Synthesis of Pyrano[3,2-c]coumarin

A mixture of a selected chalcone (0.5 mmol), 4-hydroxycoumarin (0.5 mmol), and iodine (0.5 mmol) was dissolved in 2–3 mL acetic acid. Then, the mixture was

stirred under reflux at 100 °C for the time indicated in Table 1. The reaction mixture was cooled to room temperature and diluted with water, followed by $Na_2S_2O_3 \cdot H_2O$ solution to quench excess iodine. The reaction mixture was filtered invacuo, and the residue was purified by column chromatography on silica gel (100–200mesh) using hexane/EtOAc (10:2 to 10:1, v/v) as eluent to give the pure product.

Selected Spectral Data

2,4-Diphenylpyrano[3,2-*c*]chromen-5(4*H*)-one(1) (Table 2). White solid; yield: 0.172 g (98%); mp = 168–170 °C (lit.[14] mp 173–175 °C); IR ν_{max} (KBr, cm^{-1}) 2949, 2860 (aromatic C-H str), 1709 (C=O str); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.01 (d, J = 8.0 Hz, 1H), 7.73–7.70 (m, 2H), 7.59–7.55 (m, 1H), 7.46–7.40 (m, 6H), 7.35–7.28 (m, 4H), 5.83 (d, J = 5.0 Hz, 1H), 4.72 (d, J = 4.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 161.4, 155.8, 152.8, 147.0, 143.6, 132.7, 132.0,129.3, 128.7 (2C), 128.6 (2C), 128.5 (2C), 127.2, 124.7 (2C), 124.2, 122.7, 116.8, 114.6, 103.8, 103.7, 36.7; ESI-MS m/z (%) $C_{24}H_{16}O_3$: 375 (100) [M + Na].

2-(4-Nitrophenyl)-4-p-tolylpyrano[3,2-*c*]chromen-5(4*H*)-one (14) (Table 2). Light yellow solid; yield: 0.184 g (90%); mp = 235–237 °C; IR $\boldsymbol{\nu}_{max}$ (KBr, cm^{-1}) 2983, 2891 (aromatic C-H str), 1724 (C=O str), 1545 (-NO_2str); ^{1}H NMR (500 MHz, $CDCl_3$) **δ** (ppm): 8.32 (d, J = 7.0 Hz, 2H), 8.0 (d, J = 7.0 Hz, 1H), 7.90–7.88 (m, 2H), 7.60 (m, 1H), 7.42 (m, 2H), 7.35 (m, 2H), 7.14 (d, J = 7.0 Hz, 2H), 6.05 (d, J = 5.0 Hz, 1H), 4.72 (d, J = 5.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 161.1, 155.3, 152.8, 147.8, 144.9, 139.8, 138.6, 137.4, 132.3, 129.5, 128.3 (2C), 127.3 (2C), 125.3 (2C), 124.4 (2C),124.2, 124.1, 122.5, 117.2, 117.0, 114.2, 107.2, 103.6, 36.4, 21.1; ESI-MS m/z (%) $C_{25}H_{17}NO_5$: 412(100) [M + H].

9-Bromo-2,4-diphenylpyrano[3,2-*c*]chromen-5(4*H*)-one (21) (Table 2). Light yellow solid; yield: 0.204 g (95%); mp = 220–222 °C; IR ν_{max} (KBr, cm^{-1}) 2992, 2851 (aromatic C-H str), 1719 (C=O str); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.10 (d, J = 6.0 Hz, 1H), 7.71 (m, 2H), 7.65 (dd, J = 2.0, 7.0 Hz, 1H), 7.49–744 (m, 3H), 7.32 (m, 3H), 7.28 (m, 2H), 7.23 (m, 2H), 5.84 (d, J = 5.0 Hz, 1H), 4.70 (d, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 161.1, 155.7, 152.7, 147.2, 143.5, 132.6, 132.2, 129.5, 128.8 (2C), 128.6 (2C), 127.6 (2C), 126.5, 124.3 (2C), 124.1, 121.9, 116.3, 113.9, 102.8, 102.4, 36.2; ESI-MS m/z (%) $C_{24}H_{15}BrO_3$: 453 (100) [M + Na].

9-Chloro-4-(4-chlorophenyl)-2-phenylpyrano[3,2-*c*]chromen-5(4*H*)-one (28) (Table 2). Light yellow solid; yield: 0.195 g (93%); mp = 194–196 °C; IR ν_{max} (KBr, cm^{-1}) 2920, 2870 (aromatic C-H str), 1714 (C=O str); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.90 (d, J = 7.0 Hz, 1H), 7.64 (m, 2H), 7.39–734 (m, 5H), 7.27 (m, 2H), 7.22 (m, 1H), 5.74 (d, J = 5.0 Hz, 1H), 4.66 (d, J = 5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 160.6, 154.5, 151.3, 147.2, 142.2, 134.5, 134.0, 133.1, 129.8, 129.4 (2C), 128.5 (2C), 125.1(2C), 124.6 (2C), 122.8, 118.5, 116.9, 116.3, 104.0, 103.5, 36.5; ESI-MS m/z (%) $C_{24}H_{14}Cl_2O_3$: 443(100) [M + Na].

ACKNOWLEDGMENTS

We thank the Department of Science and Technology, New Delhi, for financial support and the Department of Chemistry, Indian Institute of Technology Roorkee for the Ministry of Human Resource Development fellowship to B. V. B.

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