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Note

An excellent protocol for the synthesis of benzopyrans using basic resin under MWI

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A convenient, microwave promoted novel protocol for the synthesis of diverse kinds of substituted benzopyrans from the corresponding variety of substituted hydroxy acetophenones and keto compounds using Amberlite IRA 400 resin (basic resin) under solvent-free conditions, has been developed. This protocol is mild and more efficient than the other reported methods.

Keywords: Amberlite, benzopyran, microwave irradiation, resin, acetophenone.

Interesting chemistry is associated with chromans, chromones and chromanones and these form the core ring structure found in a number of natural products like flavanoids, isoflavanoids, coumarins, homo-, iso- and neo-flavonoids[1,2]. Compounds representing these types of classes are manifested with a variety of remarkable biological activities such as anti-allergic activity, tyrosine kinase inhibitory activity, estrogen receptor agonist or antagonist activity or inhibitor activity of steroidegenic enzymes[3,4]. Chromones/chromanones or in simple terms benzopyranones can be potential intermediates for the synthesis of heterocyclic analogs of steroids and or important building blocks for the preparation of pterocarpans and isoflavones with strong fungicidal activity[5].

2-*H*-1-Benzopyrans, commonly known as 2*H*-benzopyrans or 2*H*-chromines, are an important structural motif present in a variety of biologically active natural, synthetic drugs and lead molecules[6]. Interesting chemistry have been exploited to this structural unit for generating diverse series of compounds, have displayed a wide spectrum of potential biological activities such as anti-cancer[7], anti-diabetic[8], anti-HIV[9], anti-inflammatory[10], anti-microbial[11], anti-bacterial[12], anti-arrhythmatic[13], anti-estrogenic[14] *etc*. Moreover, their use in the synthesis of various kinds of dyes[15] and agrochemicals[16] are well known. Their major use in the development of diverse kinds of potassium channel openers have made further interest for benzopyran chemistry[17]. Furthermore, benzopyran unit has been further explored as an useful synthon for the generation of diverse kinds of pharmaceutically important complex heterocycles of natural as well as synthetic molecules[18].

Traditional syntheses of substituted benzopyrans involves the reaction of substituted hydroxyl acetophenones with keto compounds using variety of strong bases[19]. Recently, their synthesis have further achieved through different kinds of starting materials using variety of metallic and non-metallic basic catalysts either by intra-molecular cyclo-addition reactions[20] or by condensation reactions[21] from the variety of the starting substrates. Furthermore, their solid phase syntheses using various kinds of metallic system were also reported recently[22]. Most of these methods suffer from the limitations such as long reaction times, use of expensive strongly basic reagents, tedious work-up and low yields. Consequently, there is continued interest in developing new and convenient methods for the synthesis of substituted benzopyrans using mild reaction conditions. Nowadays, microwave assisted synthesis has become as important tool for the synthesis of various kind of heterocycles[23].

In continuation of our recent work[24] towards the development of novel protocols for the synthesis of substituted benzopyrans for the exploration of potentially biologically active leads, while exploring the various transformations using basic resin[25], we have invented a novel protocol for the syntheses of substituted benzopyrans using Amberlite resin (basic resin). Thus, in the present note, we report herein a novel microwave promoted, one-pot solvent-free protocol for the synthesis of substituted benzopyrans through the direct reaction of corresponding substituted acetophenones and keto-compounds mediated by basic resin.

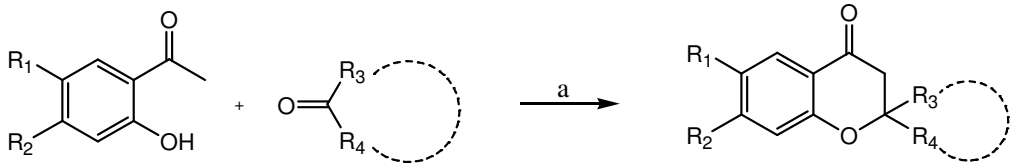
Results and Discussion

Initially, the syntheses of various substituted benzopyrans were achieved from the corresponding hydroxy acetophenones and keto-compounds using

Table I — Conversion of various substituted hydroxyacetophenones into benzopyrans of general formula **I**[a]

Entry	R^1	R^2	R^3	R^4	Time (min)	Isolated yields (%)
1	H	H	CH_3	CH_3	5	86
2	H	OH	CH_3	CH_3	5	89
3	H	OH	CH_3	C_2H_5	8	85
4	H	OH	R^3= R^4=	Cyclopentyl	7	88
5	H	OH	R^3= R^4=	Cyclohexyl	6	90
6	OH	H	CH_3	CH_3	10	81
7	OH	H	CH_3	C_2H_5	8	82
8	OH	H	R^3= R^4=	Cyclopentyl	8	89
9	OH	H	R^3= R^4=	Cyclohexyl	8	86
10	NO_2	H	CH_3	CH_3	9	85
11	OCH_3	H	CH_3	CH_3	5	91
12	OCH_3	OH	CH_3	CH_3	5	92
13	OCH_3	OCH_3	CH_3	C_2H_5	4	94
14	OCH_3	OCH_3	C_2H_5	C_2H_5	4	95
15	OC_2H_5	OH	CH_3	CH_3	5	91
16	OCH_3	NO_2	C_2H_5	CH_3	5	90
17	OCH_3	OCH_3	R^3= R^4=	Cyclopentyl	5	93
18	OCH_3	OCH_3	R^3= R^4=	Cyclohexyl	5	95
19	OH	OCH_3	*n*-C_4H_9	*n*-C_4H_9	5	92
20	OCH_3	OCH_3	*n*-C_3H_7	*n*-C_3H_7	5	89

[a]All the products were characterized by IR, NMR and mass spectral data



Reagents and conditions: (a) Microwave irradiation (power 800 W), 5-8 min

Scheme I

various kinds of solid support like neutral and basic alumina. Better yields of the products were obtained in by using basic alumina as a solid support. Moreover, the reaction was further carried out without using solid support where minute amount of substituted benzopyrans was observed. Keeping the basic nature of Amberlite IRA 400 resin, we have tried a reaction of hydroxy acetophenone with a keto compound, where it was realized that there is complete transformation of the starting materials into desired substituted benzopyran derivative. Moreover, the advantages associated with basic resin include easy removal from the reaction-mixture by simple filtration. Thus, various substituted hydroxyl compounds were reacted with variety of keto-compounds using Amberlite IRA 400 resin under microwave conditions to afford the clean formation of the corresponding substituted benzopyrans in good to excellent yields. Hence, it was concluded that reaction works using basic resin under solvent-free conditions and completed in very short time (5-8 min), afforded excellent yields (81-95%) of the desired substituted benzopyrans. The results are summarized in **Table I**. It was further realized that by the introduction of electron releasing groups at *para*-position leads to increase in the yields while electron withdrawing groups does not have any effect. The reaction conditions are shown in **Scheme I**.

In conclusion, we have developed a convenient and efficient protocol for the one-pot synthesis of substituted benzopyrans under microwave conditions.

Experimental Section

Melting points were determined on Buchi technical apparatus (BUCHI-510) and are uncorrected. IR spectra were recorded on a Bruker instrument VICTOR 22 as KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded using 200 and 500 MHZ Bruker spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard. Alumina (basic) and basic resin were purchased from Glaxo Lab., Mumbai. For thin layer chromatography, silica gel coated Aluminum sheets F_{254} (E. Merck) were used. Microwave irradiation was carried out in a domestic microwave oven at 800W.

General procedure

Substituted hydroxyacetophenone (0.01 mole) was added to a mixture of corresponding ketone (0.01 mole) and basic resin (0.02 mole). The reaction-mixture was irradiated under microwave at 800 W in a sealed tube. Resin was filtered and filtrate was concentrated to afford the desired substituted benzophenone derivative.

2,2-Dimethyl-chroman-4-one, 1: m.p. 85-87°C; IR (KBr): 2978, 1690, 1604, 1573, 1456, 1371, 1329, 1304, 1257, 1227, 1202, 1169, 1144, 1117, 1058, 1021, 955, 927, 893, 835, 806, 768, 729, 649, 604, 569 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.48 (6H, s, CH_3), 2.75 (2H, s, CH_2), 6.90-7.28 (1H, m, 6 & 8-H), 7.40-7.56 (1H, m, 7-H), 7.91 (1H, dd, *J* = 8.5 Hz & 2.5 Hz, 5-H); ^{13}C NMR (500 MHz, $CDCl_3$): δ = 26.49, 48.74, 79.40, 118.18, 120.87, 126.36, 128.48, 136.00, 160.02, 192.12; MS: *m/z* %: 176(100), 161(100), 121(100), 92(100), 63(87), 41(48); Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.976; H, 6.8640. Found: C, 75.061; H, 6.8730.

7-Hydroxy-2,2-dimethyl-chroman-4-one, 2: m.p. 168°C; IR (KBr) : 3469, 1652, 1611, 1570, 1492, 1459, 1428, 1415, 1380, 1346, 1316, 1312, 1306, 1248, 1202, 1129, 1117, 1104, 1016, 964, 932, 901, 863, 856, 814, 787, 753, 702, 618 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.43 (6H, s, 2 × CH_3), 2.63 (2H, s, CH_2), 6.90 (1H, d, *J* = 2.5 Hz, 8-H), 6.56 (1H, dd, *J* = 8.5 Hz & 2.5 Hz, 6-H), 7.83(1H, d, *J* = 8.5 Hz, 5-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.78, 48.55, 79.13, 103.44, 110.14, 114.0, 128.42, 163.12, 164.90, 192.89; MS: *m/z* %: 192(51), 177(99), 137(100), 108(58), 80(22); Anal: Calcd for $C_{11}H_{12}O_3$: C, 68.735; H, 6.2926%. Found: C, 68.809; H, 6.3010%.

2-Ethyl 7-hydroxy-2-methyl-chroman-4-one, 3: m.p. 98°C; IR (KBr) **:** 3128, 2965, 1648, 1574, 1489, 1376, 1353, 1313, 1253, 1182, 1161, 1105, 1026, 997, 950, 906, 879, 840, 816, 778, 710, 671, 641, 609, 564, 517 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 6.5 Hz, CH_3), 1.40 (3H, s, CH_3), 1.73 (2H, q, *J* = 6.5 Hz, CH_2), 2.73 (2H, s, CH_2), 6.53 (1H, d, *J* = 2.5 Hz, 8-H), 6.53 (1H, dd, *J* = 8.5 & 2.5 Hz, 6-H), 7.90 (1H, d, *J* = 8.5 Hz, 5-H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 7.90, 23.44, 32.13, 46.69, 81.38, 103.65, 110.05, 113.30, 128.66, 162.00, 164.86, 192.10; MS: *m/z* %: 206(22), 191(10), 177(52), 151(26), 137(100), 136(20), 108(19), 81(8), 69(10), 53(11), Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.944; H, 6.846 %, Found: C, 69.884, H, 6.8421%.

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