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Microwaves Assisted Fast and Clean O-alkylation of 3-hydroxychromones in Aqueous Medium

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Abstract

In this study, green and convenient method has been developed for the O-alkylation of various 3-hydroxychromones with different alkylating agents in aqueous medium to afford a variety of 3-alkoxychromones through microwave irradiation. This method offers the advantages such as higher yields, shorter reaction time and environmentally benign reaction conditions. The use of water, which is non-toxic, non-flammable and high microwave-absorbing properties, as a medium in combination with microwave irradiations for these alkylation reactions is unprecedented. This greener alternative is found to be a very useful and powerful method to construct C–O bond in chromones without using organic solvent within few seconds.

Keywords: 3-hydroxychromones; alkylation reactions; aqueous medium; microwave irradiations.

1. Introduction

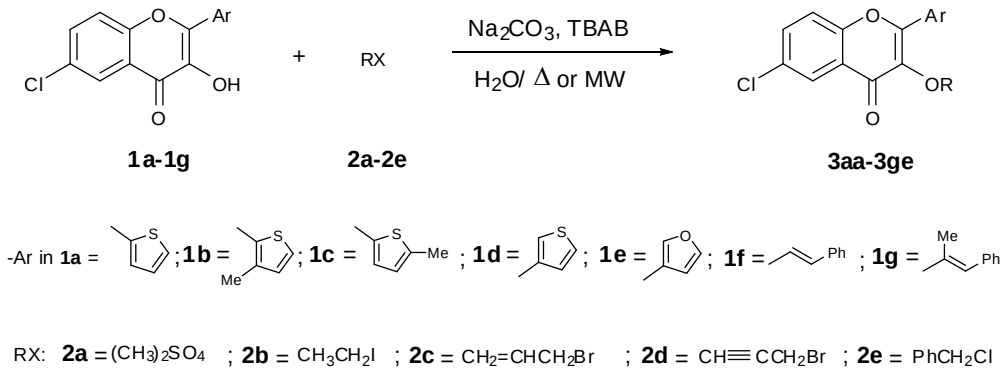
The use of water as a solvent for organic synthesis has attracted great interest and emerged as major solution for the development of economical, clean and environment-benign chemical processes (Mehdi et al, 2010; Rao et al, 2010). Water is non-toxic, readily available, non-flammable and also displayed unique reactivity and selectivity different from traditional organic solvents (Manabe et al, 2002; Li, 2005). As a part of the ‘‘green’’ concept, the classical sources of heating are often replaced by microwave (MW) heating (Lew et al, 2002; Jia et al, 2006). Water is known to be one of the best microwave-absorbing medium due to its very high dielectric constant and intermediate value for the dielectric loss. Because of these compatible properties water is frequently used in combination with microwave irradiation (Sunita et al, 2008; Carpita and

Ribecai, 2009). The aim of the present work is to apply this green methodology for the O-alkylation of 3-hydroxychromones (3HC) to afford 3-alkoxychromones.

Chromones (Harborne, 1994), an important family of oxygen heterocyclic compounds, are present in most of the parts of many plants along with their synthetic analogies, and possess a variety of biological activities (Davis et al, 1989; Jovanovic et al, 1994). Many chromone derivatives, especially 3-alkoxychromones, are photo-labile and endured various photo-induced reactions affording diverse spirocyclic (Gupta et al, 2007; Kamboj et al, 2011) and polycyclic compounds (Kamboj et al, 2011), and were prepared by the O-alkylation of 3-hydroxychromones. These alkylation reactions were carried out in acetone as solvent (Gupta et al, 1991, 2004), and suffered of some limitations: long reaction times, large solvent amounts and work-up difficulty. So, herein, we wish to report an environment-friendly and economical procedure for the O-alkylation of 3-hydroxychromones in water.

2. Results and Discussion

The reaction of 3-hydroxychromone **1a** and benzyl chloride **2e**, as model reaction system, was screened to optimize reaction conditions for the synthesis of 3-benzyloxychromone **3ea** (Scheme 1), and the results are summarized in Table 1. In the beginning, reaction was investigated using Na_2CO_3 as a base and water as a solvent under reflux condition on a hot plate with magnetic stirring; no reaction occurred (entry 1, Table 1), may be due to solubility problem. Addition of tetra-n-butylammonium bromide (TBAB) as a phase transfer catalyst (PTC) to the reaction system made the reaction feasible, and found that the reaction was completed within 20 min (TLC) to yield the desired alkylated product **3ae** (71%, entry 2, Table 1). It was characterized by its melting point, IR and ^{1}H NMR data. To increase the energy efficiency, the heating source (hot plate) was then replaced by microwave (MW) for this reaction that resulted in a remarkable enhancement in the reactions rate from minutes to few seconds in higher yields (entries 3-11, Table 1). After screening the different PTCs and various bases (entries 3-11, Table 1), the combination of TBAB (1.0 equiv) with Na_2CO_3 (1.0 equiv) was found to be the optimal for the reaction under MW conditions, in which 91% yield of product was obtained (entry 4, Table 1).



Scheme 1: Synthesis of 3-alkoxychromones 3aa-3ge.

Table 1: Optimization of reaction conditions for **3ea**.

Entry	PTC	Condition/Base	Time	Yield (%)
1	-----	Δ /Na_2CO_3	60 min	-----
2	TBAB/0.5 eq	Δ /Na_2CO_3	20 min	71
3	TBAB/0.5 eq	MW/Na_2CO_3	15 sec	78
4	TBAB/1.0 eq	MW/Na_2CO_3	15 sec	89
5	TBAB/1.5 eq	MW/Na_2CO_3	15 sec	81
6	TBAI/1.0 eq	MW/Na_2CO_3	15 sec	82
7	CTAB/1.0 eq	MW/Na_2CO_3	15 sec	69
8	TBAB/1.0 eq	MW/K_2CO_3	15 sec	86
9	TBAB/1.0 eq	MW/Et_3N	50 sec	43
10	TBAB/1.0 eq	MW/C_5H_5N	50 sec	51
11	TBAB/1.0 eq	MW/NaOH	15 sec	28

TBAI: tetra-*n*-butylammonium iodide; CTAB: cetyltrimethylammonium bromide; Δ: Conventional heating

Using the optimized reaction conditions, the applicability of this protocol was then explored for alkylation of different 3-hydroxychromones (3HC: **1a-1g**) using various alkylating agents (RX: **2a-2e**) to afford various 3-alkoxychromones **3aa-3ge** (Table 2).

3. Conclusion

In conclusion, we have described the O-alkylation of various 3-hydroxychromones with different alkylating agents using tetra-n-butylammonium bromide/Na_2CO_3 and water as solvent. Use of water as reaction media coupled with microwave irradiations provided an efficient, green and economical protocol to obtain the 3-alkoxychromones. Application of microwave irradiation considerably increased the yield and rate of the reactions.

Table 2: O-Alkylation of various 3-hydroxychromones with different alkylating agents.

Entry	3HC	RX	R-	Product	Δ t (20 min) Yield (%)	MW t (15 sec) Yield (%)	Mp (^oC) Obs. / Lit.
1	1a	2a	CH_3-	3aa	86	92	132-134/135-136
2	1a	2b	CH_3CH_2-	3ab	71	82	134-136/135
3	1a	2e	$PhCH_2$-	3ae	82	91	138-140/138
4	1b	2a	CH_3-	3ba	81	95	132-134/136-138
5	1b	2c	CH_2=$CHCH_2$-	3bc	91	90	128-130/130-132
6	1b	2d	$CHCCH_2$-	3bd	89	93	158-160/156-158

7	1b	2e	$PhCH_2$-	3be	93	92	136-138/132-134
8	1c	2a	CH_3-	3ca	80	94	128-130/130
9	1c	2e	$PhCH_2$-	3ce	80	86	142-144/143-144
10	1d	2a	CH_3-	3da	80	90	140/142-143
11	1d	2c	CH_2=$CHCH_2$-	3dc	78	88	98-100/102-104
12	1d	2d	$CHCCH_2$-	3dd	85	94	146/148-150
13	1e	2a	CH_3-	3ea	81	91	112-114/114-117
14	1e	2b	CH_3CH_2-	3eb	80	87	100-102/104-106
15	1e	2c	CH_2=$CHCH_2$-	3ec	77	88	92-94/93-95
16	1e	2d	$CHCCH_2$-	3ed	86	93	122-124/121-123
17	1e	2e	$PhCH_2$-	3ee	70	84	90-92/86-89
18	1f	2a	CH_3-	3fa	75	85	164-166/168
19	1f	2c	CH_2=$CHCH_2$-	3fc	76	89	128-130/134
20	1f	2e	$PhCH_2$-	3fe	82	91	146-148/144-146
21	1g	2a	CH_3-	3ga	85	93	88-92/90-92
22	1g	2c	CH_2=$CHCH_2$-	3gc	76	87	60-64/62-63
23	1g	2e	$PhCH_2$-	3ge	81	92	68-70/72-74

Lit. Mp(^{0}C)-(Gupta et al, 1991, 2004; Kamboj et al, 2009a,b, 2011, 2012)

4. Experimental

4.1 General

Reactions were carried out with a 1200W (600W used) microwave oven (BPL-Sanyo, INDIA). Melting points were determined in open capillaries and are thus uncorrected.

4.1.1 Typical experimental procedure (microwave)

6-Chloro-3-hydroxy-2-(thiophen-2-yl)-4H-chromen-4-one **1a** (0.557g, 1.0 equiv), Na_2CO_3 (0.106g, 1.0 equiv) and TBAB (0.636g, 1.0 equiv) were mixed in a mortar with pestle. This mixture was transferred to a small beaker containing benzyl chloride **2e** (0.278g, 1.1 equiv) and then suspended in 10 ml water. The suspension was irradiated with microwaves for 15 sec under 600 W power. The reaction mixture was allowed to cool at room temperature and a solid mass was obtained. The solid obtained was filtered, dried and recrystalized with methanol to obtain the pure white product, **3ae**.

4.1.2 Typical experimental procedure (conventional)

Mixed the 6-chloro-3-hydroxy-2-(thiophen-2-yl)-4H-chromen-4-one **1a** (0.557g, 1.0 equiv), Na_2CO_3 (0.106g, 1.0 equiv) and TBAB (0.636g, 0.1 equiv) in a mortar with pestle. This mixture was transferred to a round bottom flask containing benzyl chloride **2e** (0.278g, 1.1 equiv) and 10 ml water, and then refluxed on a hot plate with magnetic stirring. After completion of the reaction (20min, TLC), the reaction mixture was cooled at room temperature. The solid obtained was then filtered, dried and recrystalized with methanol to afford **3ae**.

4.1.3 Selected spectral data

3ba: IR ν_{max} (cm^{-1}): 1643.0 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.24 (1H, d, J = 2.4 Hz), 7.62 (1H, dd, J = 2.4 Hz, J = 9.0 Hz), 7.53 (1H, d, J = 5.1 Hz), 7.46 (1H, d, J = 9.0 Hz), 7.00 (1H, d, J = 5.1 Hz), 3.99 (3H, s), 2.66 (3H, s); ^{13}C NMR ($CDCl_3$): δ 172.84, 153.14, 141.83, 139.46, 133.46, 131.66, 130.74, 130.12, 125.33, 125.16, 124.57, 119.28, 77.19, 59.96, 17.33; Mass (m/z): 307 (M+1).

3bd: IR ν_{max} (cm^{-1}): 1636.3 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.23 (1H, d, J = 2.7), 7.63 (1H, dd, J = 2.7 Hz, J = 9.0 Hz), 7.55 (1H, d, J = 5.1 Hz), 7.48 (1H, d, J = 9.0 Hz), 7.00 (1H, d, J = 5.1 Hz), 5.07 (2H, d, J = 2.4 Hz), 2.65 (3H, s), 2.40 (1H, t, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$): δ 172.50, 153.22, 152.10, 142.10, 141.00, 133.62, 131.47, 130.87, 130.27, 129.80, 125.15, 124.78, 119.36, 76.59, 76.33, 59.03, 17.39; Mass (m/z): 331 (M+1).

3bc: IR ν_{max} (cm^{-1}): 1643 (C=O), 1605 (C=C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.23 (1H, d, J = 2.4 Hz), 7.61 (1H, dd, J = 2.4 Hz, J = 9.0 Hz), 7.52 (1H, d, J = 5.1Hz), 7.46 (1H, d, J = 9.0 Hz), 7.00 (1H, d, J= 5.1 Hz), 6.07 (1H, ddt, J = 6.6 Hz, J = 17.4 Hz, J = 10.8 Hz), 5.37 (1H, dd, J = 1.5 Hz, J = 17.4 Hz), 5.23 (1H, dd, J = 10.5 Hz, J = 1.2 Hz), 4.76 (2H, d, J = 6.6 Hz), 2.64 (3H, s); ^{13}C NMR ($CDCl_3$): δ 172.87, 154.07, 153.12, 141.83, 137.87, 133.44, 133.21, 131.54, 130.69, 129.99, 125.20, 125.12, 124.76, 119.31, 119.18, 72.99, 17.36; Mass (m/z): 333 (M+1).

3be: IR ν_{max} (cm^{-1}): 1628.0 (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.26 (1H, d, J = 2.4 Hz), 7.62 (1H, dd, J = 2.4 Hz, J = 8.7 Hz), 7.42-7.46 (3H, m), 7.49 (1H, d, J = 5.1 Hz), 7.39-7.28 (3H, m), 6.93 (1H, d, J = 5.1 Hz), 5.22 (2H, s), 2.55 (3H, s); ^{13}C ($CDCl_3$): δ 172.95, 154.14, 153.21, 141.82, 138.13, 136.40, 133.48, 131.32, 130.73, 129.91, 128.95, 128.22, 125.27, 125.12, 124.83, 119.38, 73.75, 17.11; Mass (m/z): 383 (M+1).

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References

[1] A C Waiss, R E Lundin, A Lee and J Corse (1967), *J. Am. Chem. Soc*., **89**, pp. 6213-6218.

[2] A Carpita and A Ribecai (2009), *Tetrahedron Lett*., **50**, pp. 6877-6881.

[3] A Lew, P O Krutzik, M E Hart and A R Chamberlin (2002), *J. Comb. Chem*., **4**, pp. 95–105.

[4] A Mehdi, E Sheikhi, A Kavoosi and H R Bijanzadeh (2010), *Tetrahedron*, **66**, pp. 9263-9269.

[5] C J Li (2005), *Chem. Rev*., **105**, pp. 3095-3165.

[6] C S Jia, Z Zhang, S J Tu and G W Wang (2006), *Org. Biomol. Chem*., **4**, pp. 104-110.

[7] J B Harborne (1993), *The Flavanoids-Advances in Research since 1986,* Chapman and Hall, London.
[8] K Manabe, S Limura, X M Sun and S J Kobyashi (2002), *Am. Chem. Soc*., **124**, pp. 11971-11978.
[9] P Sunitha, K S Kumar, B R Rao and G Venkateshwarlu (2008), *Green Chem. Lett. Rev*., **1**, pp. 179-183.
[10] R C Kamboj, G Sharma, D Kumar and R Arora (2012), *C. R. Chimie*, **15**, pp. 311-316.
[11] R C Kamboj, M Thakur, R Arora, S Berar, U Berar and S C Gupta (2009), *J. Indian Chem. Soc*., **86**, pp. 388-392.
[12] R C Kamboj, R Arora, D Kumar and G Sharma (2012), *J. Photochem. Photobiol. A: Chem*., **220**, pp. 124-133.
[13] R C Kamboj, S Berar, U Berar, M Thakur and S C Gupta (2009), *J. Photochem. Photobiol. A: Chem*., **204**, pp. 122–128.
[14] R C Kamboj, U Berar, S Berar, M Thakur, R Arora and S C Gupta (2009), *Can. J. Chem*., **87**, pp. 422-429.
[15] R H Davis, M G Leitner, J M Russo and M E Byrne (1989), *J. Am. Podiatr Med. Assoc*., **79**, pp. 263-276.
[16] S C Gupta, M Thakur, S Sharma, U Berar, S Berar and R C Kamboj (2007), *Beil. J. Org. Chem*., **3**, pp. 14.
[17] S C Gupta, M Yusuf, S Sharma, A Saini, S Arora and R C Kamboj (2004), *Tetrahedron*, **60**, pp. 8445-8454.
[18] S C Gupta, S Sharma, A Saini, S N Dhawan (1991), *J. Chem Soc. Perkin Trans I*, pp. 2391-2395.
[19] S V Jovanovic, S Steenken, M Tosic, B Marjanovic and M G Simic (1994), *J. Am. Chem. Soc*., **116**, pp. 4846-4851.
[20] V K Rao, S S Reddy, B S Krishna, K R M Naidu and C N Raju (2010), *Green Chem. Lett. Rev*., **3**, pp. 217-223.