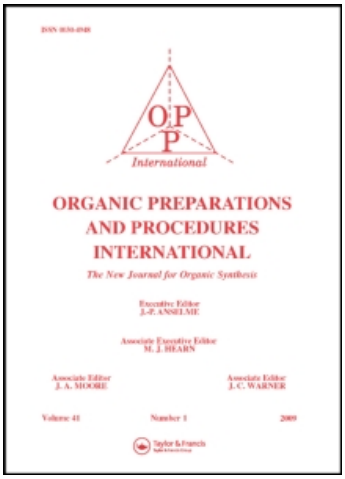

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A CONVENIENT SYNTHESIS OF 2-METHYL-3-SUBSTITUTED-4(3*H*)-QUINAZOLINONES USING *BIS*(TRICHLOROMETHYL) CARBONATE AS CONDENSING AGENT

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A CONVENIENT SYNTHESIS OF 2-METHYL-3-SUBSTITUTED-4(3*H*)-QUINAZOLINONES USING *bis*(TRICHLOROMETHYL) CARBONATE AS CONDENSING AGENT

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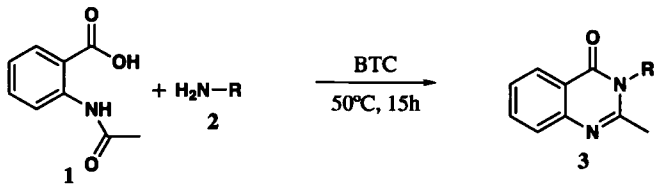
4(3*H*)-Quinazolinones are well known as antihypertensive, antidiabetic, antiinflammatory, anticonvulsant, and antibacterial agents.[1] Some of the compounds are natural products.[2] Thus, many synthetic methods have been reported. The simplest and most straightforward procedure was developed by Niementowski in 1895[3] and improved by Grimmel *et al.* in 1946[4] who reported that 4(3*H*)-quinazolinones could be synthesized from *N*-acetylanthranilic acids and anilines in toluene or xylene using phosphorus trichloride or phosphorus oxychloride as condensing agents. However, the condensing agents used are toxic and difficult to handle. Other methods, such as the reactions of *N*-arylnitrilium salts with isocyanates,[5] of 2-nitrobenzyl chloride with arylamines[6] and of 2-aminobenzonitriles with urea-hydrogen peroxide,[7] have also been reported. Again, most of these procedures have such disadvantages as low yields and difficult handling. Over the past decades, *bis*(trichloromethyl) carbonate (BTC) in organic synthesis has received great interest as a versatile synthetic auxiliary, because of its lower vapor pressure, higher stability and safer handling.[8] In continuation of our interest in the studies of BTC,[9] we now report the application of BTC as the condensing agent for the preparation of 2-methyl-3-substituted-quinazolinones from *N*-acetylanthranilic acid **1** and amines **2** under mild conditions (*Scheme 1*).



a) R = C_6H_5; b) R = *p*-(CH_3)C_6H_4; c) R = *m*-(CH_3)C_6H_4; d) R = *o*-(CH_3CH_2)C_6H_4; e) R = *p*-(NO_2)C_6H_4; f) R = *p*-ClC_6H_4; g) R = *o*-ClC_6H_4; h) R = *m*-ClC_6H_4; i) R = *p*-(CH_3CH_2O)C_6H_4; j) R = $C_6H_5CH_2$; k) R = $CH_3CH_2CH_2$

Scheme 1

We found that the amount of BTC plays a pivotal role in the yield of the corresponding products. As mentioned in a review,[8] symmetrical ureas are produced in good yields when BTC reacts with an excess of primary amines. We investigated the effect of the amount of BTC,

hoping to identify an optimal combination that could minimize the side-reactions and provide higher yields of 2-methyl-3-substituted-4(3*H*)-quinazolinones. We studied the reaction of aniline and *N*-acetylanthranilic acid in the present of various amounts of BTC (*Table 1*). This study demonstrated that 1/3 equivalent of BTC is sufficient to convert one equivalent of substrate **1** to 4(3*H*)-quinazolinones. Another important factor is reaction temperature, and 50°C is sufficient to carry out the conversion. In comparison with reported methods using other condensing agents,[3,4,10] our procedure can be carried out safely under mild conditions. With respect to the scope and limitation of the synthesis of 2-methyl-3-substituted-4(3*H*)-quinazolinones using our improved protocol, several amines were reacted with *N*-acetylanthranilic acid under similar conditions, and the results were summarized in *Table 2*. In general, yields were good. Anilines gave better yields than propylamine and benzylamine. Although Xue[10] has reported that no 4(3*H*)-quinazolinone was produced in the reaction involving an alkylamine in the present of phosphorus trichloride, we did obtain the corresponding products even using propylamine or benzylamine in moderate yields (**3j** and **3k** in *Table 2*, 65% and 53%, respectively).

In conclusion, 2-methyl-3-substituted-4(3*H*)-quinazolinones can be synthesized conveniently and in good yields using BTC as condensing reagent under mild reaction conditions.

Table 1. Reaction of Aniline with *N*-Acetylanthranilic Acid(**1**)

Entry	Solvents	Ratio of BTC:**1**	Temp. (°C)	Yield (%)[a]
1	CH_3CN	1:6	50	15
2	CH_3CN	1:3	50	78
3	CH_3CN	1:2	50	30
4	CH_3CN	1:3	60	65
5	CH_3CN	1:3	40	67
6	CH_3CN	1:3	r.t.	21
7	THF	1:3	50	23

a) Yields based on N-acetylanthranilic acid.

EXPERIMENTAL SECTION

N-acetylanthranilic acid[11] **1** was prepared from *o*-aminobenzoic acid which was obtained from Aldrich. All other chemicals and solvents used were also purchased from Aldrich. Melting points were obtained on a capillary melting point apparatus and are uncorrected. ^1H NMR spectra ($CDCl_3$) were determined on a Varian Mercur plus-400 spectrometer using TMS as internal standard. MS spectra were recorded on a Finnigan Trace DSQ Mass spectrometer at an ionization potential of 75eV. IR spectra were measured on a Thermo Nicolet AVATAR 370 FT-IR spectrometer. Preparative TLC separations were carried out with silica gel GF-254 coated glass plates, using the solvents specified in the procedure.

Table 2. Preparation of 4(3*H*)-Quinazolinones using BTC[a]

Cmpd	Yield (%)[b]	mp. (°C)	*lit.* (°C)	MS(EI) m/z (%)	IR(C=O) (cm^{-1})	^1H NMR (δ)
3a	78	146	145-146[12]	237(M^++1, 32) 236(M^+, 52) 77(100)	1678	8.28 (1H, dt, *J* = 8.0 and 0.8 Hz, ArH), 7.80-7.76 (1H, m, ArH), 7.69 (1H, d, *J* = 8.0 Hz, ArH), 7.59-7.46 (4H, m, ArH), 7.28-7.26 (2H, m, ArH), 2.26 (3H, s, CH_3)
3b	81	149	148-150[12]	251(M+1, 35) 250(M^+, 84) 91(100)	1686	8.28 (1H, d, *J* = 8.0 Hz, ArH), 7.80-7.75 (1H, m, ArH), 7.70 (1H, d, *J* = 7.6 Hz, ArH), 7.48 (1H, t, *J* = 7.6 Hz, ArH), 7.36 (2H, d, *J* = 8.0 Hz, ArH), 7.14(2H, d, *J* = 7.6 Hz, ArH), 2.45 (3H, s, CH_3), 2.27 (3H, s, CH_3)
3c	71	127	126[13]	251(M+1, 48) 250(M^+, 100)	1674	8.28 (1H, dd, *J* = 8.0 and 0.8 Hz, ArH), 7.79-7.75 (1H, m, ArH), 7.68 (1H, d, *J* = 7.6 Hz, ArH), 7.49-7.42 (2H, m, ArH), 7.31 (1H, d, *J* = 7.6 Hz, ArH), 7.06 (2H, d, *J* = 8.8 Hz, ArH), 2.43 (3H, s, CH_3), 2.26 (3H, s, CH_3)
3d	75	80	81[14]	265(M+1, 27) 264(M^+, 46) 249(100)	1683	8.29 (1H, dd, *J* = 8.0 and 1.2 Hz, ArH), 7.80-7.76 (1H, m, ArH), 7.70 (1H, d, *J* = 7.6 Hz, ArH), 7.50-7.46 (3H, m, ArH), 7.40-7.35(1H, m, ArH), 7.15 (1H, d, *J* = 7.6 Hz, ArH), 2.46-2.40 (2H, m, CH_2), 2.20 (3H, s, CH_3), 1.20-1.16 (3H, m, CH_3)
3e	75	189	190-193[4]	282(M+1, 25) 281(M^+, 100)	1680	8.47-8.43 (2H, m, ArH), 8.27 (1H, dd, J = 8.0 and 1.2 Hz, ArH), 7.84-7.79 (1H, m, ArH), 7.71 (1H, d, J = 7.6 Hz, ArH), 7.53-7.47 (3H, m, ArH), 2.26 (3H, s, CH_3)
3f	83	155	156-158[4]	272(M+2, 32) 271(M+1, 36) 270(M^+, 100)	1689	8.27 (1H, dd, *J* = 7.6 and 0.8 Hz, ArH), 7.80-7.76 (1H, m, ArH), 7.69 (1H, d, *J* = 8.0 Hz, ArH), 7.56-7.53 (2H, m, ArH), 7.50-7.46 (1H, m, ArH), 7.23-7.20 (2H, m, ArH), 2.26 (3H, s, CH_3)
3g	81	127	126-127[15]	272(M+2, 12) 271(M+1, 25) 270(M^+, 30) 235(100)	1682	8.29 (1H, d, *J* = 8.8 Hz, ArH), 7.81-7.77 (1H, m, ArH), 7.70 (1H, d, *J* = 8.0 Hz, ArH), 7.64-7.62 (1H, m, ArH), 7.51-7.46 (3H, m, ArH), 7.36-7.34 (1H, m, ArH), 2.24 (3H, s, CH_3)

Table 2. Continued...

Cmpd	Yield (%)[b]	mp. (°C)	*lit.* (°C)	MS(EI) m/z (%)	IR(C=O) (cm^{-1})	^1H NMR (δ)
3h	77	130	129-131[15]	272(M+2, 37) 271(M+1, 53) 270(M^+, 100)	1686	8.27 (1H, dd, *J* = 7.2 and 1.2 Hz, ArH), 7.81-7.77 (1H, m, ArH), 7.69 (1H, d, *J* = 8.0 Hz, ArH), 7.52-7.47 (3H, m, ArH), 7.32-7.30 (1H, m, ArH), 7.20-7.17 (1H, m, ArH), 2.27 (3H, s, CH_3)
3i	79	155	155-156.5[16]	281(M+1, 40) 280(M^+, 100)	1686	8.27 (1H, dd, *J* = 8.0 and 1.2 Hz, ArH), 7.78-7.66 (2H, m, ArH), 7.48-7.44 (1H, m, ArH), 7.16-7.14 (2H, m, ArH), 7.06-7.03 (2H, m, ArH), 4.10 (2H, q, *J* = 7.2 Hz, CH_2), 2.26 (3h, s, CH_3), 1.46 (3H, t, *J* = 7.2 Hz, CH_3)
3j	65	231	230-232[17]	251(M+1,40) 250(M^+, 100)	1674	8.32 (1H, d, *J* = 8.0 Hz, ArH), 7.78-7.74 (1H, m, ArH), 7.66 (1H, d, *J* = 8.8 Hz, ArH), 7.48 (1H, t, *J* = 8.0 Hz, ArH), 7.35-7.28 (3H, m, ArH), 7.20 (2H, d, *J* = 7.2 Hz, ArH), 5.41 (2H, s, CH_2), 2.57 (3H, s, CH_3)
3k	53	80	81-82[18]	203(M+1,11) 202(M^+, 57) 160(100)	1672	8.24 (1H, dd, *J* = 8.0 and 1.2 Hz, ArH), 7.73-7.69 (1H, m, ArH), 7.61 (1H, d, *J* = 8.0 Hz, ArH), 7.43 (1H, t, *J* = 7.6 Hz, ArH), 4.07-4.03 (2H, m, CH_2), 2.65 (3H, s, CH_3), 1.80-1.74 (2H, m, CH_2), 1.03 (3H, t, *J* = 7.2 Hz, CH_3)

a) Substrate **1** (3 mmol), amines **2** (4 mmol), BTC (1 mmol) and CH_3CN (10 mL) was used.
b) Yields based on Substrate **1**.

Typical Procedure.- To a flask fitted with a thermometer, condenser and stirrer containing *N*-acetylanthranilic acid (0.54 g, 3 mmol) and acetonitrile (10 mL), was added aniline (0.37 mL, 4 mmol). After ten minutes, BTC (0.30 g, 1 mmol) was added at room temperature. The reaction mixture rapidly became exothermic. Then the suspension was heated to 50°C and stirring maintained at this temperature for 15 hr. The mixture was evaporated to an oily residue which was dissolved in dichloromethane (10 mL). Then the solution was extracted with 10% sodium hydrogen carbonate solution (5 mL) and the organic layer was separated and dried over anhydrous magnesium sulfate. Removal of the solvents under vacuum gave a residue which was subjected to chromatographic purification on preparative TLC (cyclohexane:ethyl acetate, 1:1 v/v) to give 2-methyl-3-phenyl-4(3*H*)-quinazolinone in 78% yield.

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SYNTHESIS OF OCTANDRENOLONE, FLEMICULOSIN, (±)-3-DEOXY-MS-II AND LAXICHALCONE

Submitted by Mandar Deodhar, David StC Black and Naresh Kumar*
(09/21/05)

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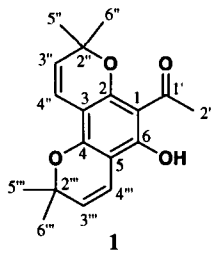
Flavonoids are widely distributed in the plant kingdom and play a vital role in the ecology of plants. Many flavonoids have been shown to possess a wide range of biological activities including antioxidant,[1] anticancer,[2] anti-inflammatory[3] and antiviral.[4]



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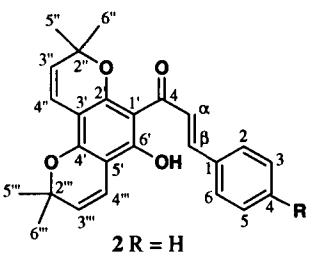

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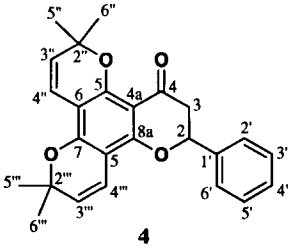

4

Octandrenolone (**1**) was first isolated from the leaves of *Melicome octandra*[5] and later from *Melicope erromangensis*.[6] The related chalcone structure flemiculosin (**2**), was isolated from leaves of *Flemengia fruticulosa*[7] and its structure was confirmed by X-ray crystallography.[8] A closely related analogue laxichalcone (**3**), was isolated from the roots of *Derris laxiflora* and