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A one-pot synthesis of 3,3′-methylenebis(2-arylamino-4*H*-chromen-4-one) from C-(4-oxo-4*H*-1-benzopyran-3-yl)-*N*-arylnitrone

Sourav Maiti, Suman Kalyan Panja, Chandrakanta Bandyopadhyay *

Department of Chemistry, R. K. Mission Vivekananda Centenary College, Rahara, Kolkata 700 118, West Bengal, India

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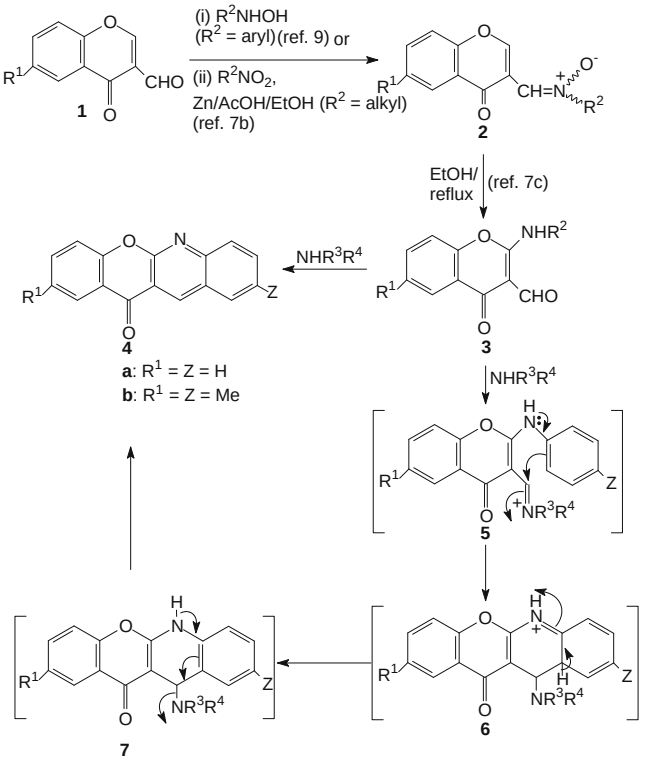
ABSTRACT

2-(Arylamino)-4-oxo-4*H*-chromene-3-carbaldehyde **3** (R^2 = aryl) produces 12*H*-chromeno[2,3-*b*]quinolin-12-one **4** when treated with sarcosine, piperidine or diethylamine, but produces 3,3′-methylenebis(2-arylamino-4*H*-chromen-4-one) **8** when treated with the same amine in the presence of an excess of formaldehyde. Compound **3** (R^2 = alkyl) was found to be less reactive than the *N*-aryl analogues towards the deformylative Mannich-type reaction.

Pharmaceutical activities of bisbenzopyrans depend on the position of attachment of two benzopyran rings. Bisbenzopyrans coupled through 3- and 3′-positions have drawn much attention in recent years because of their applications in different fields. 3,3′-Biscoumarinylketones are used as dyes and pigments, fluorescent brighteners and photographic sensitizers.[1] Some members of 3,3′-bisbenzopyran family act as non-peptide HIV-1 protease inhibitors,[2] monoamine oxidase (MAO) inhibitors[3] and anticoagulant agents.[4] Coupling between 3- and 3′-positions of two benzopyran rings by a methylene bridge has been achieved by the reaction of formaldehyde on 4-hydroxycoumarin.[5] Synthesis of methylene-bridged bisnaphthopyrans has been reported by using Mannich-type reaction on 3-*N*,*N*-dimethylamino-1*H*-naphtho[2,1-*b*]pyran-1-one in acetic acid.[6]

In continuation with our earlier studies on nitrones **2** derived from 4-oxo-4*H*-chromene-3-carbaldehyde (commonly known as 3-formylchromone) **1**[7] and on the deformylative Mannich-type reaction on **1**,[8] we were interested in studying the deformylative Mannich-type reaction on 2-(alkyl/arylamino)-4-oxo-4*H*-chromene-3-carbaldehyde **3**, which can readily be obtained from nitrone **2** (Scheme 1).[7c,9] Although some chemistry of 2-amino-4-oxo-4*H*-chromene-3-carbaldehyde and 2-(*N*,*N*-dialkylamino)-4-oxo-4*H*-chromene-3-carbaldehyde has been studied,[10,11] chemistry of 2-(alkyl/arylamino)-4-oxo-4*H*-chromene-3-carbaldehyde **3** is little explored. Most of the work on **3** was carried out by convert-



Scheme 1. Synthesis of 12*H*-chromeno[2,3-*b*]quinolin-12-one **4**.[7a,13]

* Corresponding author. Tel.: +91 3325925125.
E-mail address: kantachandra@rediffmail.com (C. Bandyopadhyay).

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Table 1
Results of the reactions of **3** with 2°-amines in the presence or absence of formaldehyde

Entry	R^1	R^2	2°-Amine (R^3R^4NH)	Additive	Solvent	Time (h)	Product (% yield)	Mps (°C)
1	H	Ph	Sarcosine	—	EtOH	6	N.R.[b]	—
2	H	Ph	Sarcosine	—	DMF	2	**4a** (70)	236–238
3	Me	Ar[a]	Sarcosine	—	DMF	2	**4b** (72)	260–262
4	H	Ph	Piperidine	—	DMF	1	**4a** (90)	236–238
5	H	Ph	Piperidine	—	EtOH	2	**4a** (92)	236–238
6	H	Ph	Et_2NH	—	EtOH	2	**4a** (89)	236–238
7	H	Ph	PhNHMe	—	EtOH	10	N.R.[b]	—
8	H	Ph	Sarcosine	CH_2O	MeOH	10	N.R.[b]	—
9	Me	Ph	Sarcosine	CH_2O	EtOH	10	N.R.[b]	—
10	H	Ph	Sarcosine	CH_2O	AcOH	10	Not isolated	—
11	H	Ph	Sarcosine	CH_2O	MeCN	12	**8a** (10)	300–302
12	H	Ph	Sarcosine	CH_2O	DMF	1	**8a** (65)	300–302
13	Me	Ar[a]	Sarcosine	CH_2O	DMF	1	**8b** (79)	304–306
14	Me	Ph	Sarcosine	CH_2O	DMF	1	**8c** (70)	268–270
15	H	Ph	Sarcosine	CH_2O	Me_2CO	40	N.R.[b]	—
16	H	Ph	—	CH_2O	DMF	6	N.R.[b]	—
17	H	Ph	Piperidine	CH_2O	DMF	0.5	**8a** (90)	300–302
18	H	Ph	Piperidine	CH_2O	EtOH	2.5	**8a** (58)	300–302
19	Me	Ar[a]	Et_2NH	CH_2O	DMF	0.5	**8b** (92)	304–306
20	H	Ph	Et_2NH	CH_2O	EtOH	1	**8a** (60)	300–302
21	H	Ph	Piperidine	$(CH_2O)_n$[c]	EtOH	3.5	**8a** (30)	300–302
22	Me	Et	Sarcosine	CH_2O	EtOH	11	N.R.[b]	—
23	Me	Me	Sarcosine	CH_2O	DMF	5	N.R.[b]	—
24	Me	Et	Piperidine	CH_2O	EtOH	20	N.R.[b]	—
25	Me	Me	Piperidine	CH_2O	DMF	7	**8d** (40)	>320
26	Me	Et	Piperidine	CH_2O	DMF	8	**8e** (42)	258–260
27	H	Et	Piperidine	CH_2O	DMF	7	**8f** (45)	254–256

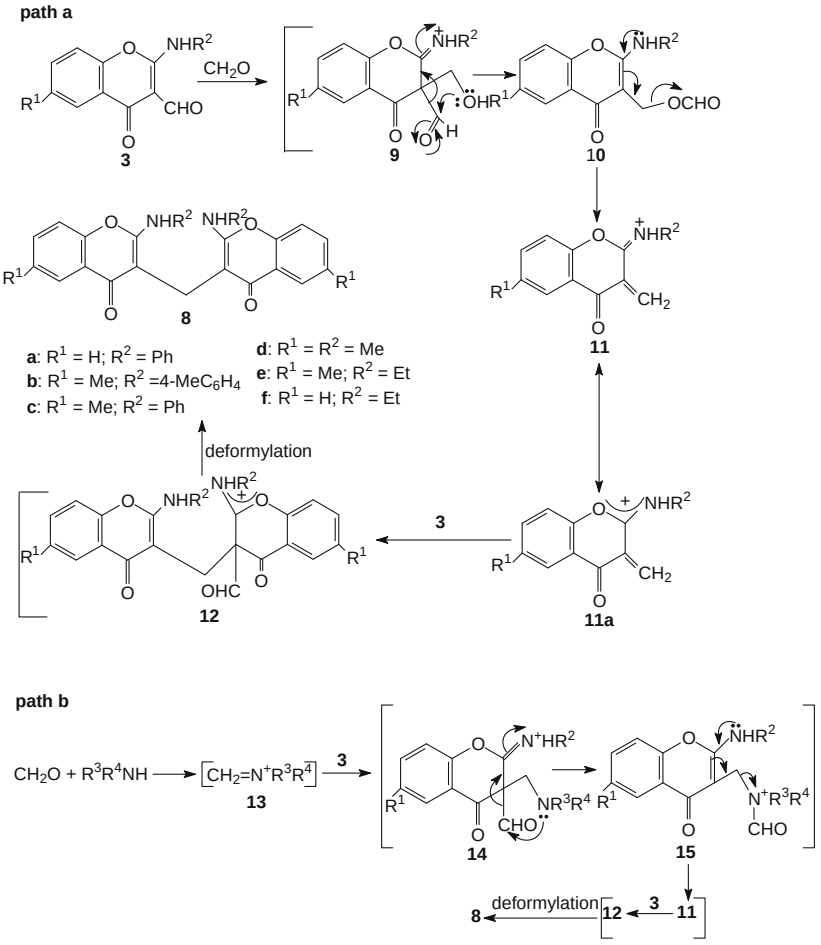
[a] Ar stands for 4-MeC_6H_4.
[b] N.R. stands for no reaction.
[c] Paraformaldehyde.

ing it into N,N-disubstituted analogue by alkylation.[11a,c,d] Formation of Schiff-bases from **3** involving primary diamines,[11a] and reaction of **3** with ethyl (triphenylphosphoranylidene)acetate for the synthesis of a chromenopyridine have been reported.[11d] The reaction of *N*-methylglycine (sarcosine) with **1** has been studied under different reaction conditions.[12] We report herein the results of the reaction of **3** with secondary amines in the presence or absence of formaldehyde.

Although no change was observed when compound **3** was heated under reflux with equimolar amounts of sarcosine in ethanol for 6 h (Table 1, entry 1), the same reaction mixture led to the formation of chromenoquinolone **4** on heating in DMF instead of in ethanol at 80–100 °C for 2 h (entries 2 and 3). Transformation of **3** to **4** has earlier been achieved by treating **3** with $AlCl_3$ followed by H_2SO_4[9] or only with H_2SO_4.[7a,13] Assuming the secondary amine function in sarcosine to be responsible for this cyclization reaction (Scheme 1), compound **3** was heated with piperidine in DMF and surprisingly, the conversion was accomplished within 1 h (entry 4). The same conversion could also be achieved in excellent yield by heating **3** with piperidine or diethylamine in ethanol for 2 h (entries 5 and 6). The yellow solid **4** can be isolated simply by filtration from the reaction mixture after cooling. The formation of **4** from **3** may be rationalized as follows. Aldehyde function of **3** reacts with secondary amine to produce the iminium ion **5**, which then induces cyclization to **4** via **6** and **7** (Scheme 1). It has to be mentioned here that the weaker nucleophile *N*-methylaniline fails to carry out this transformation even after heating for 10 h in ethanol (entry 7). This process for the formation of **4** from **3** compares well with the earlier reports.[7a,9,11a,13]

As an extension of our recent report on the deformylative Mannich-type reaction,[8] the above results gave us an impetus to study how this aldehyde **3** would behave with secondary amines in the presence of formaldehyde. So, an equimolar mixture of **3** and sarcosine was heated in methanol or ethanol in the presence of excess amount of 37% aqueous formaldehyde solution for 10 h, but no change in **3** was observed (entries 8 and 9). No pure compound could be isolated by making the medium acidic by using acetic acid as solvent (entry 10). However, by heating in acetonitrile for 12 h, small amount of a white solid **8** was isolated along with unreacted **3** (50%) (entry 11). Considering the necessity of a polar aprotic solvent, the reaction was carried out in DMF and the reaction mixture showed the absence of **3** (by TLC) only after heating for 1 h. After usual work-up, compound **8** was obtained in 60–80% yield (entries 12–14). But in acetone, a relatively low boiling polar aprotic solvent, no change in **3** was observed even after heating for 40 h (entry 15).

The structure of the compound **8** was determined on the basis of IR, ^1H NMR, ^{13}C NMR and mass spectral analysis.[14] The formation of **8** may be rationalized by either of the two pathways: (a) hydroxymethylation of **3** (→**9**) followed by formyl transfer (→**10**) and elimination of formic acid to generate Michael acceptor **11**, which is intercepted by the enamine moiety of **3** to produce **12**. This on subsequent deformylation gives **8** (Scheme 2, path (a) or (b) initially formed iminium ion **13** is involved in Mannich-type reaction to form **14**, which can also produce the Michael-type acceptor **11** via **15** and finally produces **8** (path b). To check the necessity of amine, compound **3** was heated with excess formaldehyde in DMF for 6 h, but compound **3** remained unchanged (entry 16), which rules out path a. In support of path b, compound **3** was heated in DMF with piperidine (instead of with sarcosine) in the presence of excess aqueous formaldehyde solution. The reaction completed within 30 min with an excellent yield of **8** (entry 17). Interestingly on performing this reaction in ethanol instead of in DMF, the reaction was complete in 2.5 h with a moderate yield, (entry 18), but use of sarcosine instead of piperidine in alcohol failed to show any change (entries 8 and 9). Use of diethylamine instead of piperidine also produced similar results (entries 19 and 20), but use of paraformaldehyde instead of aqueous formaldehyde required more time and gave poor yield of **8** (entry 21).



Scheme 2. Synthesis of 3,3′-methylenebis(2-*N*-alkyl-/arylamino-4*H*-chromen-4-one) **8**.

Having an insight on the transformation of **3** to **8**, attempts were made to synthesize **8** directly from nitrone **2** in a one-pot reaction. Nitrone **2** (R^2 = aryl) was heated in ethanol for 2 h, then piperidine (1 equiv) and 37% aqueous formaldehyde solution (excess) were added and heating was continued for another 3 h. Indeed, the reaction mixture produced **8** in good to excellent yield.[15] This sequential one-pot reaction involves rearrangement of nitrone **2** to aminoaldehyde **3**,[7c,9] and a tandem Mannich-type reaction, Michael reaction and deformylation reaction. It is worth mentioning that when nitrone **2**, piperidine and formalin were all taken together and heated either in ethanol or in DMF, the yield of **8** was quite low (20–25%).

The deformylative Mannich-type reaction was then applied to **3** (R^2 = alkyl). Surprisingly, the reactions with *N*-alkyl derivatives are very slow. Compound **3** (R^1 = Me; R^2 = Et, Me) failed to react with sarcosine in ethanol or DMF (entries 22 and 23). It failed to react even with piperidine in ethanol (entry 24), but it reacted with piperidine in DMF to produce **8** (entries 25–27). The lesser reactivity of **3** (R^2 = alkyl) in comparison to that of **3** (R^2 = aryl) towards the formation of **8** may be due to a competitive formation of iminium ion involving the alkylamino group of **3** (R^2 = alkyl) and formaldehyde, but it could not be ascertained.

In conclusion, we have developed a new convenient method for the cyclization of **3** (R^2 = aryl) to **4** and also synthesized bischromone **8** from nitrone **2** by a sequential one-pot reaction involving a deformylative Mannich-type reaction. Extension of this synthetic strategy towards new biologically active heterocycles is in progress.

Acknowledgments

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14. *3,3′-Methylenebis(2-N-phenylamino-4H-chromen-4-one)* **8a**: White fine crystalline solid, Anal. Calcd for $C_{31}H_{22}N_2O_4$: C, 76.53; H, 4.56; N, 5.76. Found: C, 76.33; H, 4.40; N, 5.61. IR (KBr) ν_{max}: 3438, 3048, 2758, 1654, 1605, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (2H, s, CH_2), 7.13–7.23 (2H, m, ArH), 7.30–7.49 (8H, m, ArH), 7.53–7.70 (6H, m, ArH), 8.30 (2H, br d, J = 7.8 Hz, 2×5-H), 12.02 (2H, s, exchangeable, 2 × N–H); ^{13}C NMR ($CDCl_3$) δ 18.3, 100.3, 116.5, 121.3, 122.4, 124.1, 124.9, 125.5, 129.1, 132.1, 138.2, 152.7, 160.6, 176.7; mass *m/z*: 487 (M^++H), 509 (M^++Na).
15. *General procedure for the synthesis of* ***8*** *in a one-pot reaction*: Nitrone **2** (R^2 = aryl) (1 mmol) was heated under reflux in ethanol (25 mL) for 2 h and complete conversion of **2** to **3** was observed by TLC. Under this condition, piperidine (85 mg, 1 mmol) and 37% aqueous formaldehyde solution (1.5 mL) were added to the reaction mixture and heated under reflux for another 3 h, when a white solid separated out. The solid was filtered and crystallized from benzene–petroleum ether (10:1) to afford **8** in 80–90% yields.