A New Synthesis of Flavanones

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Received 7 March 1997; revised 6 June 1997

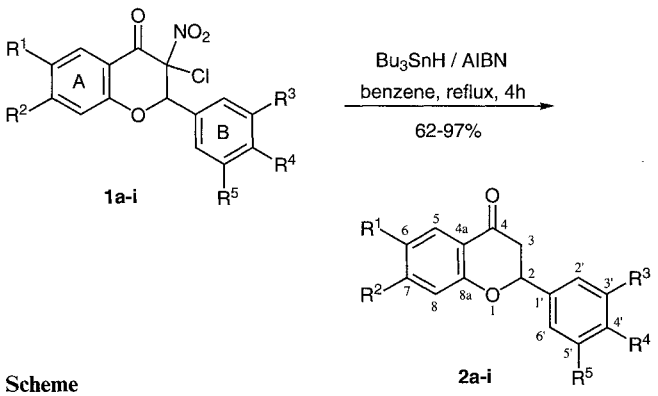
Flavanones **2** were synthesized in good yields from 3-chloro-2,3-dihydro-3-nitro-2-phenyl-4*H*-1-benzopyran-4-ones **1** using a free radical process involving the tributyltin hydride/2,2′-azobisisobutyronitrile system in refluxing benzene.

Flavanones (2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one derivatives) are pivotal biosynthetic precursors for major flavonoids such as flavones or isoflavones, and for two important flavonoid intermediates: the flavan-4-ols (biosynthetic precursors for the formation of 3-deoxyanthocyanins) and the dihydroflavonols (biosynthetic intermediates in the formation of catechins, flavonols, anthocyanins and proanthocyanidins).[1] The flavanone skeleton is present in a wide range of synthetic or naturally occurring products exhibiting various interesting pharmacological activities.[2] Furthermore, it is worth pointing out that this important class of heterocyclic compounds, since the first authoritative book edited by Geissman in 1962,[3] has been periodically reviewed from both chemical and biological viewpoints.[4]

The methodology most commonly adopted to prepare flavanones involves the isomerization of appropriately substituted 2′-hydroxychalcones. These cyclizations have been carried out under numerous conditions using acids,[5] bases,[5a,5c,5e,6] silica gel,[6g,7] heat,[8] light,[9] electrolysis,[10] a nickel chloride/zinc/potassium iodide reagent system,[11] cobalt(II) Schiff-base complexes[12] or zeolites,[13] but the obtained yields are often moderate and sometimes poor. To our knowledge, only three alternative procedures employing direct precursors other than chalcones have been reported. They consist of oxidizing flavan-4-ols,[14] reacting benzaldehydes with 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones in basic medium,[15] and in transforming 3-bromo-1-phenylprop-2-ynyl aryl ethers in the presence of mercury(II) trifluoroacetate.[16]

A few years ago, we described a convenient and general method to synthesize 3-chloro-2,3-dihydro-3-nitro-2-phenyl-4*H*-1-benzopyran-4-ones **1** starting from variously substituted benzaldehydes and salicylaldehydes.[17] These benzopyranones **1** have already proved to be valuable intermediates to provide access to 3-nitroflavones,[17b] then to 3-aminoflavones.[18] We now report that compounds **1** are also, in most cases, suitable starting materials for the preparation of flavanones **2**.

As tributyltin hydride (TBTH) is well known to be able to replace either aliphatic halogens[19] or aliphatic nitro groups[19b,20] by hydrogen atoms in a radical chain process initiated by 2,2′-azobisisobutyronitrile (AIBN), the present one-pot synthesis has been based on the use of these reagents in refluxing benzene to abstract both the chlorine atom and the nitro substituent on the sp^3 carbon in the 3-position of **1** (Scheme).



Scheme

1–2	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	H
b	H	H	H	Cl	H
c	H	H	H	F	H
d	H	H	H	OCH_3	H
e	H	H	OCH_3	OCH_3	H
f	H	H	OCH_3	OCH_3	OCH_3
g	Cl	H	H	Cl	H
h	OCH_3	H	H	Cl	H
i	H	OCH_3	H	Cl	H

The reaction conditions and the relative proportions of reagents have been optimized using the 4′-chloro derivative as starting material. We particularly ascertained that longer reaction times or the use of toluene as solvent instead of benzene leads to lower yields.

The results summarized in Table 1 illustrate that the herein described reduction procedure is compatible with a large range of substituents and provides good yields. It must still be pointed out that when the above reaction was carried out with benzopyranones **1** bearing an aromatic nitro group on either ring A (6-position) or ring B (2′-, 3′- or 4′-position), a complex mixture was obtained. Since aromatic nitro groups, in several instances, have been reported to be recovered unchanged in the presence of the TBTH/AIBN system,[19b,21] we have no rational explanation for the unexpected behavior observed in our context. However, a recent communication of Bonjoch and co-workers, dealing with the total synthesis of the indole alkaloid Tubifolidine, reports the use of the same system to perform a reductive heterocyclization involving an aromatic nitro group.[22] Added to the verification made for the present work that 4-nitroanisole (selected as a very simple representative of aromatic nitro compounds) is almost completely transformed into a complex mixture of products under our reaction conditions, the above literature example is illustrative of the fact that

Table 1. Flavanones **2** Prepared

Product[a]	Yield[b] (%)	mp (°C)[d]		MS (CI, NH_3) *m/z*
		found	reported (Lit.)	
2a	97	75–76	74–76[6a]	225 $(M+H)^+$ 242 $(M+NH_4)^+$
2b	91	95–96	94–95[6d]	259, 261 $(M+H)^+$ 276, 278 $(M+NH_4)^+$
2c	93	78–79	79–80[23]	243 $(M+H)^+$ 260 $(M+NH_4)^+$
2d	94	88–89[e]	88–89[14e]	255 $(M+H)^+$ 272 $(M+NH_4)^+$
2e	88	124–125	125[9d]	285 $(M+H)^+$ 302 $(M+NH_4)^+$
2f	81	131–132	131–133[9d]	315 $(M+H)^+$ 332 $(M+NH_4)^+$
2g	62[c]	152–153	135–136[24]	293, 295, 297 $(M+H)^+$ 310, 312, 314 $(M+NH_4)^+$
2h	87	119–120		289, 291 $(M+H)^+$ 306, 308 $(M+NH_4)^+$
2i	84	124–125	122[25]	289, 291 $(M+H)^+$ 306, 308 $(M+NH_4)^+$

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.28; H, ±0.10.
[b] Yield of pure isolated product based on **1**.
[c] In this case, uncharacterized less polar material was formed.
[d] The following solvents were used for recrystallization: pentane **(2b)**, hexane **(2a,c,d,g,h)** and heptane **(2e,f,i)**.
[e] This melting point, although it remained constant after two successive recrystallizations, is not consistent with some values (94–98 °C) reported in the literature.[6g,15,26] A similar observation has already been pointed out by Hoshino and co-workers.[27]

aromatic nitro groups are not as inert towards the TBTH/AIBN system as generally claimed.

In summary, a large range (with the exception of aromatic nitro compounds) of the biologically important title compounds **2** can be prepared in a one-flask novel procedure starting from 3-chloro-2,3-dihydro-3-nitro-2-phenyl-4*H*-1-benzopyran-4-ones **1**. This new route to flavanones **2** is based on the previously described broad accessibility to the 3-chloro-3-nitro derivatives **1** derived from salicylaldehydes and benzaldehydes.[17,18]

Melting points were measured on a Köfler hot stage apparatus and are uncorrected. Mass spectra were obtained with a Nermag-Ribermag R10-10C spectrometer applying a desorption chemical ionization technique (CI) using NH_3 as the reagent gas. Infrared spectra were registered with a Perkin-Elmer 1710 spectrophotometer as $CHCl_3$ solutions. The ^1H NMR (300 MHz) and ^{13}C NMR (75.45 MHz) spectra were recorded on a Bruker AC 300 spectrometer. Chemical shifts are expressed in ppm downfield from TMS. With regard to ^1H NMR, splitting patterns have been designated as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet), br. (broad signal). Coupling constants (*J* values) are listed in Hertz (Hz). Microanalyses were carried out by the "Service Central d'Analyse du C.N.R.S., Vernaison, France". Reactions were monitored by analytical thin layer chromatography performed on Merck 60 F 254 precoated plates and products were visualized by UV light. Merck Silica gel (230–400 Mesh ASTM) was used for column chromatography. CH_2Cl_2 and acetone employed as eluents were distilled on a rotary evaporator prior to use. Anhydrous benzene was obtained by distillation from CaH_2. Tributyltin hydride and AIBN were purchased from Aldrich Chemical Co. and were used without further purification. The starting 3-chloro-2,3-dihydro-3-nitro-2-phenyl-4*H*-1-benzopyran-4-ones **1a–i** were prepared according to the formerly reported procedure.[17,18]

2,3-Dihydro-2-phenyl-4*H*-1-benzopyran-4-ones (Flavanones) 2; General Procedure:

The appropriate 3-chloro-2,3-dihydro-3-nitro-2-phenyl-4*H*-1-benzopyran-4-one **1** (2 mmol) was dissolved in anhydrous benzene (30 mL), under Ar atmosphere, in a 50 mL two-necked round bottom flask equipped with a condenser, a magnetic bar and a septum inlet. To the obtained solution, AIBN (411 mg, 2.5 mmol) was added in one portion before the flask was immersed in a thermostated oil bath (temperature of the bath: 100 °C). From the outset of the reflux, tributyltin hydride (2.33 g, 2.15 mL, 8 mmol) was quickly added to the stirred solution via a syringe (the medium became instantaneously yellow). The reflux was continued for 3 h whilst the mixture turned gradually to bright green then, in some cases, to brown-green. After cooling, the solvent was distilled under reduced pressure using a rotary evaporator and maintaining the temperature below 50 °C (excessive heating must be avoided because sublimation occurred on some occasions). The residue was taken up with MeCN (60 mL) and hexane (20 mL). After decantation, the lower MeCN phase was extracted with hexane (4 × 15 mL) in order to remove most of the tin derivatives. The MeCN solution was then evaporated to dryness, and the crude material obtained was flash-chromatographed over a silica gel column (100 g, eluent CH_2Cl_2 for **2a–d** and **2g–i** or CH_2Cl_2/acetone 96:4 for **2e** and **2f**) to provide pure flavanone which was further recrystallized in the appropriate solvent (Tables 1 and 2).

We thank the "Centre National de la Recherche Scientifique" and "Institut Curie" for financial support of this work. We also express our gratitude to Geneviève Flad for recording the ^1H NMR, ^{13}C NMR and infrared spectra.

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Table 2. Spectral Data of Flavanones **2**

Product	IR ($CDCl_3$) ν C=O (cm^{-1})	^1H NMR (300 MHz) ($CDCl_3$/TMS) δ, J (Hz)	^{13}C NMR (75.45 MHz) ($CDCl_3$/TMS) δ[a]
2a	1688	2.87–3.16 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.91$, $J_{AX} = 3.0$, $J_{AB} = 16.8$, $\delta_B = 3.11$, $J_{BX} = 13.6$); 5.47–5.53 (X part of ABX system, 1H, $CHCH_2$); 7.04–7.10 (m, $2H_{arom}$); 7.40–7.60 (m, $6H_{arom}$); 7.95 (dd, 1H, H-5, $J = 2.0$, 8.1)	44.7 (C-3); 79.6 (C-2); 118.2 (C-8); 120.9 (C-4a); 121.7 (C-6); 126.3 (C-2′, C-6′); 127.2 (C-5); 128.8 (C-4′); 128.9 (C-3′, C-5′); 136.2 (C-7); 138.9 (C-1′); 161.6 (C-8a); 191.7 (C-4)
2b	1693	2.84–3.12 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.89$, $J_{AX} = 2.7$, $J_{AB} = 16.8$, $\delta_B = 3.05$, $J_{BX} = 13.3$); 5.44–5.51 (X part of ABX system, 1H, $CHCH_2$); 7.03–7.10 (m, $2H_{arom}$); 7.40–7.48 (AA′BB′ system, 4H, H-2′, H-3′, H-5′, H-6′); 7.53 (dt, 1H, H-7, $J = 1.8$, 7.9); 7.93 (dd, 1H, H-5, $J = 1.8$, 7.8)	44.5 (C-3); 78.7 (C-2); 118.0 (C-8); 120.8 (C-4a); 121.7 (C-6); 127.0 (C-2′, C-6′); 127.4 (C-5); 128.9 (C-3′, C-5′); 134.4 (C-4′); 136.2 (C-7); 137.2 (C-1′); 161.2 (C-8a); 191.4 (C-4)
2c	1688	2.85–3.09 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.89$, $J_{AX} = 2.7$, $J_{AB} = 16.9$, $\delta_B = 3.07$, $J_{BX} = 13.5$); 5.46–5.52 (X part of ABX system, 1H, $CHCH_2$); 7.04–7.27 (m, $4H_{arom}$); 7.45–7.56 (m, $3H_{arom}$); 7.95 (dd, 1H, H-5, $J = 1.7$, 7.7)	44.7 (C-3); 79.0 (C-2); 115.7 (C-3′, C-5′); 118.2 (C-8); 121.0 (C-4a); 121.8 (C-6); 127.1 (C-5); 128.1 (C-2′, C-6′); 136.3 (C-1′, C-7); 161.5 (C-8a); 164.9 (C-4′); 191.7 (C-4)
2d	1690	2.84–3.18 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.88$, $J_{AX} = 2.7$, $J_{AB} = 16.8$, $\delta_B = 3.12$, $J_{BX} = 13.3$); 3.85 (s, 3H, OCH_3); 5.41–5.48 (X part of ABX system, 1H, $CHCH_2$); 6.97 and 7.43 (AA′BB′ system, 4H, H-2′, H-3′, H-5′, H-6′); 7.03–7.09 (m, $2H_{arom}$); 7.51 (dt, 1H, H-7, $J = 1.5$, 7.8); 7.94 (dd, 1H, H-5, $J = 1.5$, 7.8)	44.5 (C-3); 55.4 (OCH_3); 79.4 (C-2); 114.3 (C-3′, C-5′); 118.2 (C-8); 121.0 (C-4a); 121.6 (C-6); 127.1 (C-5); 127.8 (C-2′, C-6′); 130.9 (C-1′); 136.2 (C-7); 160.1 (C-4′); 161.7 (C-8a); 192.2 (C-4)
2e	1688	2.85–3.19 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.89$, $J_{AX} = 2.7$, $J_{AB} = 16.9$, $\delta_B = 3.13$, $J_{BX} = 13.3$); 3.91 (s, 3H, OCH_3); 3.93 (s, 3H, OCH_3); 5.41–5.47 (X part of ABX system, 1H, $CHCH_2$); 6.92 (br d, 1H, H-6′, $J = 8.6$); 7.00–7.09 (m, $4H_{arom}$); 7.52 (br t, 1H, H-7, $J = 8.6$); 7.94 (dd, 1H, H-5, $J = 1.7$, 8.1)	44.4 (C-3); 55.9 (OCH_3-3′, OCH_3-4′); 79.4 (C-2); 109.3 (C-2′); 111.0 (C-5′); 118.0 (C-8); 118.7 (C-6′); 120.8 (C-4a); 121.5 (C-6); 126.9 (C-5); 131.1 (C-1′); 136.1 (C-7); 149.1 (C-3′ or C-4′); 149.2 (C-4′ or C-3′); 161.4 (C-8a); 192.0 (C-4)
2f	1691	2.86–3.16 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.90$, $J_{AX} = 2.7$, $J_{AB} = 16.9$, $\delta_B = 3.11$, $J_{BX} = 13.5$); 3.87 (s, 3H, OCH_3); 3.91 (s, 6H, $2 \times OCH_3$); 5.39–5.45 (X part of ABX system, 1H, $CHCH_2$); 6.71 (s, 2H, H-2′, H-6′); 7.05–7.10 (m, $2H_{arom}$); 7.53 (br t, 1H, H-7, $J = 8.7$); 7.94 (dd, 1H, H-5, $J = 1.9$, 8.1)	44.6 (C-3); 56.0 (OCH_3-3′, OCH_3-5′); 60.7 (OCH_3-4′); 79.7 (C-2); 103.1 (C-2′, C-6′); 118.0 (C-8); 120.7 (C-4a); 121.5 (C-6); 126.8 (C-5); 134.2 (C-1′); 136.1 (C-7); 138.0 (C-4′); 153.3 (C-3′, C-5′); 161.3 (C-8a); 191.7 (C-4)
2g	1697	2.87–3.10 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.91$, $J_{AX} = 2.9$, $J_{AB} = 16.9$, $\delta_B = 3.04$, $J_{BX} = 13.3$); 5.43–5.49 (X part of ABX system, 1H, $CHCH_2$); 7.02 (d, 1H, H-8, $J = 8.8$); 7.39–7.43 (AA′BB′ system, 4H, H-2′, H-3′, H-5′, H-6′); 7.47 (dd, 1H, H-7, $J = 2.8$, 8.8); 7.89 (d, 1H, H-5, $J = 2$, 8)	44.3 (C-3); 79.1 (C-2); 119.7 (C-8); 121.7 (C-4a); 126.5 (C-5); 127.5 (C-6); 127.6 (C-2′, C-6′); 129.2 (C-3′, C-5′); 136.2 (C-7); 134.8 (C-4′); 136.9 (C-1′); 159.8 (C-8a); 190.4 (C-4)
2h	1687	2.83–3.07 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.87$, $J_{AX} = 3.1$, $J_{AB} = 16.9$, $\delta_B = 3.02$, $J_{BX} = 13.5$); 3.83 (s, 3H, OCH_3); 5.40–5.46 (X part of ABX system, 1H, $CHCH_2$); 6.99 (d, 1H, H-8, $J = 8.9$); 7.13 (dd, 1H, H-7, $J = 3.0$, 8.9); 7.35 (d, 1H, H-5, $J = 3.0$); 7.38–7.50 (AA′BB′ system, 4H, H-2′, H-3′, H-5′, H-6′)	44.3 (C-3); 55.7 (OCH_3); 78.8 (C-2); 107.3 (C-5); 119.3 (C-8); 120.6 (C-4a); 125.3 (C-7); 127.4 (C-2′, C-6′); 128.9 (C-3′, C-5′); 134.3 (C-4′); 137.3 (C-1′); 154.2 (C-8a); 155.8 (C-6); 191.4 (C-4)
2i	1681	2.79–3.06 (AB part of ABX system, 2H, CH_2CH, $\delta_A = 2.83$, $J_{AX} = 2.7$, $J_{AB} = 16.9$, $\delta_B = 3.00$, $J_{BX} = 13.3$); 3.85 (s, 3H, OCH_3); 5.43–5.49 (X part of ABX system, 1H, $CHCH_2$); 6.50 (d, 1H, H-8, $J = 2.2$); 6.64 (dd, 1H, H-6, $J = 2.2$, 8.8); 7.39–7.49 (AA′BB′ system, 4H, H-2′, H-3′, H-5′ H-6′); 7.88 (d, 1H, H-5, $J = 8.8$)	44.3 (C-3); 55.7 (OCH_3); 79.2 (C-2); 101.0 (C-8); 110.4 (C-6); 115.0 (C-4a); 127.6 (C-2′, C-6′); 128.8 (C-5); 129.1 (C-3′, C-5′); 134.6 (C-4′); 137.5 (C-1′); 163.3 (C-8a); 166.3 (C-7); 190.1 (C-4)

[a] The signals were assigned by comparison with a set of interpreted spectra in the flavonoid series.[28]

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