$4H$-1-Benzopyrans by a Tandem S_N2-S_NAr Reaction

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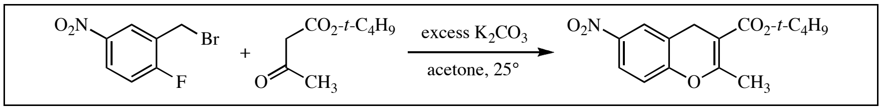

Treatment of 2-fluoro-5-nitrobenzyl bromide with active methylene compounds in the presence of excess potassium carbonate in acetone leads to the formation of highly functionalized $4H$-1-benzopyrans by a tandem S_N2-S_NAr reaction sequence. The reaction works well with β-keto esters, β-keto sulfones, β-keto phosphine oxides, β-keto phosphonates and β-keto nitriles. The reaction is simple to perform and affords products in 50-92% yields.

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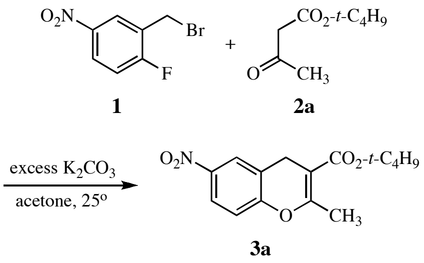
INTRODUCTION

A recent project in our laboratory required monoalkylation of a *tert*-butyl acetoacetate (**2a**) with 2-fluoro-5-nitrobenzyl bromide (**1**). Other synthetic work with dialkyl malonates had shown that potassium carbonate in acetone gave good yields of mpnoalkylation products using a 24:3:1 ratio of base:malonate:bromide at room temperature [2]. We, therefore, sought to effect a similar transformation using the β-keto ester in place of the β-diester. Attempts to perform this reaction under our standard conditions, however, led to the formation of 2-methyl-6-nitro-$4H$-1-benzopyran (**3a**) by an interesting S_N2-S_NAr process (Scheme 1). In light of the limited methodology to prepare highly functionalized $4H$-1-benzopyrans [3-6] and recent reports that several derivatives of this ring system express powerful anticancer activity [6], we sought to explore a number of active methylene substrates to determine the scope and generality of this process.

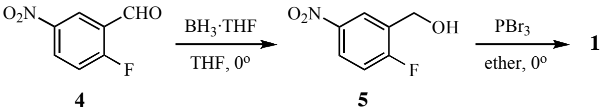
Scheme 1



RESULTS AND DISCUSSION

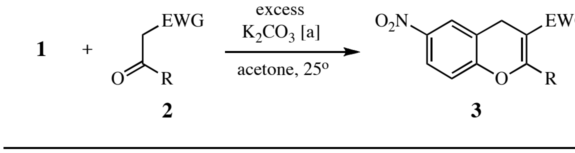
The 2-fluoro-5-nitrobenzyl bromide (**1**) used in our reactions was readily prepared in 78% overall yield from the known 2-fluoro-5-nitrobenzaldehyde (**4**) [7] by chemoselective reduction of the aldehyde with borane-tetrahydrofuran complex [8] and treatment of the resulting alcohol **5** with phosphorus tribromide (Scheme 2). With the exception of 1-(diphenylphosphinoyl)-2-propanone [9], the active methylene compounds selected for this study were commercially available.

Scheme 2



A survey of potential activated substrates **2** (R = methyl or aryl; EWG = electron withdrawing group) revealed that the reaction is favored for systems not prone to *O*-alkylation. Thus, the reaction works well with β-keto esters, β-keto sulfones, β-keto phosphine oxides, β-keto phosphonates and β-keto nitriles, generally using an 8:1:1 mole ratio of base:substrate:bromide (Table 1). On the other hand, with the exception of dibenzoylmethane, β-diketones such as 2,4-pentanedione and dimedone were found to yield primarily *O*-alkylation products while active ketones such as phenylacetone and deoxybenzoin gave exclusively monoalkylation at carbon. With appropriate substrates, the reaction is simple to perform and affords solid products in 50-92% yields.

Table 1



Entry	R	EWG	Ratio **1**:**2**	Yield of **3**
a	CH_3	CO_2-t-C_4H_9	1:3	92 [b]
b	C_6H_5	CO_2CH_3	1:1	85
c	2-Cl-C_6H_4	CO_2CH_3	1:3	52
d	CH_3	$SO_2C_6H_5$	1:1	68
e	C_6H_5	$SO_2C_6H_5$	1:1	80
f	CH_3	$P(O)(C_6H_5)_2$	1:1	70
g	CH_3	$P(O)(OCH_3)_2$	1:3	50
h	C_6H_5	CN	1:1	67
i	C_6H_5	$C(O)C_6H_5$	1:3	85 [c]

[a] 8 eq of potassium carbonate (relative to the active methylene substrate) were used. [b] For this case, an excess of the β-keto ester was required to minimize double alkylation at carbon. [c] Some *O*-alkylation product was also obtained.

The current protocol generates highly functionalized 4*H*-1-benzopyrans by an interesting tandem S_N2-S_NAr sequence. The method represents a novel 3+3 approach to these ring systems whereby the 1,3-disposed nucleophilic centers of the active methylene substrate react with the 1,3-disposed electrophilic centers of the alkylating agent (Figure 1).

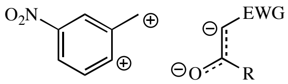
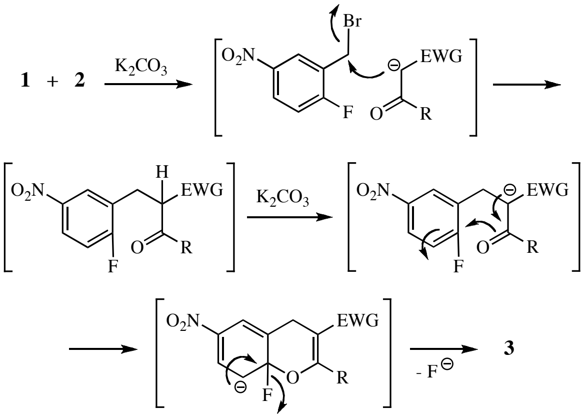


Figure 1

The mechanism of the reaction involves (1) deprotonation of the active methylene substrate, (2) S_N2 displacement of bromide from 2-fluoro-5-nitrobenzyl bromide, (3) removal of the second active proton and (4) intramolecular S_NAr displacement of fluoride by the ketone oxygen of the resulting enolate (Scheme 3).

Scheme 3



Finally, attempts to expand the scope of this process by varying the R group revealed a further limitation. For example, when methyl isobutyrylacetate (R = *i*-C_3H_7, EWG = CO_2Me) was reacted, the simple S_N2 alkylation product was isolated, but the subsequent cyclization did not occur. Based on earlier results in a related system [10], we believe that the failure to cyclize in this case results from an unfavorable steric interaction that develops as the large R group is forced into coplanarity with the ester moiety during the final ring closure. Though this finding limits the procedure from a synthetic perspective, it does provide some insight into the reaction chronology by suggesting that the S_N2 is the first step of the tandem sequence.

CONCLUSION

We have developed a new approach to the synthesis of 4*H*-1-benzopyrans based on a novel tandem S_N2-S_NAr reaction sequence. The method represents a formal 3+3 strategy and is successful for relatively unhindered active methylene substrates that favor initial *C*-alkylation of the monoanion. The reaction furnishes products as solids in 50-92% yields with a minimum of purification. The current products differ from those prepared by other methods in having a nitro group at C6. Other activating groups on the aromatic ring may also be possible and are being explored.

EXPERIMENTAL

All reactions were run under dry nitrogen in oven-dried glassware. Potassium carbonate was ground to a fine powder, dried under vacuum at 120° for 24 hours and stored in an oven at 120°; acetone (ACS Grade) was used from a freshly opened bottle. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech 21521). Preparative separations were performed by one of the following methods: (1) flash column chromatography [11] on silica gel (grade 62, 60-200 mesh) containing ultraviolet-active phosphor (Sorbent Technologies UV-5) packed into quartz columns or (2) preparative thin layer chromatography on 20-cm x 20-cm silica gel GF plates (Analtech 02015). Compound elution in all cases was monitored using a hand-held ultraviolet lamp. Hexanes used in chromatography had a boiling range of 65-70°; petroleum ether used in crystallization and trituration procedures had a boiling range of 35-60°. Melting points were uncorrected. Infrared spectra were run as thin films on NaCl disks and referenced to polystyrene. Unless otherwise indicated, ^1H and ^{13}C nuclear magnetic resonance spectra were measured in $CDCl_3$ at 400 MHz and 100 MHz, respectively, using tetramethylsilane as the internal standard; coupling constants (*J*) are given in Hertz. Mass spectra (electron impact/direct probe) were obtained at 30 electron volts. β-Keto phosphine oxide **2f** used to prepare **3f** was prepared as described by Torr and Warren [9].

2-Fluoro-5-nitrobenzyl Alcohol (**5**). A solution of 5.00 g (29.6 mmoles) of **4** [7] in 75 mL of anhydrous tetrahydrofuran was prepared and cooled to 0°. This solution was stirred and 12.0 mL of 1 *M* borane tetrahydrofuran complex (12.0 mmoles) in tetrahydrofuran [8] was added by syringe over 35 minutes. The reaction was stirred at 0° for 1 hour and at 22° for 1 hour. The reaction was quenched at 0° by slow addition of 10 mL of water, then transferred to a separatory funnel with ether and washed with saturated aqueous sodium chloride (three times). The combined ether layers were dried (magnesium sulfate) and concentrated under vacuum to give a yellow oil that solidified on standing. The product was crystallized from 50% ether in petroleum ether to give 4.89 g (97%) of **5** as light yellow crystals, mp 69-71°. ir: 3533, 1524, 1352, 1244 cm^{-1}; ^1H nmr: δ 8.42 (dd, 1H, J = 6.2, 3.0), 8.19 (ddd, 1H, J = 9.0, 4.6, 3.0), 7.19 (t, 1H, J = 9.0), 4.86 (s, 2H), 2.23 (br s, 1H); ^{13}C nmr: δ 163.5 (d, J = 257.0), 144.1, 129.7 (d, J = 17.1), 125.0 (d, J = 10.3), 124.7 (d, J = 6.9), 116.1 (d, J = 24.0), 58.3 (d, J = 4.3); ms: *m/z* 171 (M^+). *Anal.* Calcd. for $C_7H_6FNO_3$: C, 49.12; H, 3.51; N, 8.19. Found: C, 49.07; H, 3.48; N, 8.13.

2-Fluoro-5-nitrobenzyl Bromide (**1**). A solution of 4.75 g (27.8 mmoles) of **5** in 75 mL of anhydrous ether was prepared and cooled to 0°. This solution was stirred and 3.77 g (1.31 mL, 13.9 mmoles) of phosphorus tribromide was added dropwise during 1 hour. The reaction was stirred for 3 hours with gradual warming to room temperature and then poured onto crushed ice and extracted with ether (three times). The combined ether layers were washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and concentrated under vacuum to give a light yellow solid. Recrystallization from 2% ether in petroleum ether gave 5.21 g (80%) of **1** as light yellow powder, mp 73-74°. ir: 1524, 1352, 1244 cm^{-1}; ^{1}H nmr: δ 8.36 (dd, 1H, J = 6.4, 3.0), 8.22 (ddd, 1H, J = 9.0, 4.3, 3.0), 7.25 (t, 1H, J = 9.0), 4.53 (d, 2H, J = 0.8); ^{13}C nmr: δ 163.9 (d, J = 260.8), 144.2, 127.1 (d, J = 5.2, obscures a second C signal), 126.1 (d, J = 10.3), 116.9 (d, J = 24.0), 23.6 (d, J = 4.3); ms: *m/z* 233, 235 (M^{+}, M^{+}+2). *Anal.* Calcd. for $C_7H_5BrFNO_2$: C, 35.90; H, 2.14; N, 5.98. Found: C, 35.96; H, 2.17; N, 5.93.

Representative Procedure for the Cyclization of 4*H*-1-Benzopyrans. *tert*-Butyl 2-methyl-6-nitro-4*H*-1-benzopyran-3-carboxylate (**3a**). To a solution of 1.19 g (7.5 mmoles) of **2a** in 50 mL of acetone was added 8.28 g (60 mmoles) of anhydrous potassium carbonate followed by dropwise addition of a solution of 0.59 g (2.5 mmoles) of **1**. The reaction was vigorously stirred for 48 hours at room temperature, vacuum filtered through a pad of Celite$^{®}$, and concentrated under reduced pressure. The excess β-keto ester was removed under high vacuum at 40° and the resulting solid was triturated with 10% petroleum ether in ether to give 0.67 g (92%) of **3a** as a light yellow powder, mp 114-116°. ir: 1709, 1692, 1656, 1529, 1344 cm^{-1}; ^{1}H nmr: δ 8.03 (m, 2H), 6.99 (d, 1H, J = 9.9), 3.63 (s, 2H), 2.37 (t, 3H, J = 1.5), 1.53 (s, 9H); ^{13}C nmr: δ 166.0, 158.7, 154.9, 143.9, 124.8, 123.6, 122.0, 116.7, 94.4, 81.1, 28.3 (3), 25.1, 18.9; ms: *m/z* 218 (M^{+}-C_4H_9O). *Anal.* Calcd. for $C_{15}H_{17}NO_5$: C, 61.86; H, 5.84; N, 4.81. Found: C, 61.89; H, 5.87; N, 4.76.

Methyl 6-Nitro-2-phenyl-4*H*-1-benzopyran-3-carboxylate (**3b**). This compound (0.66 g, 85%) was prepared using an 8:1:1 mole ratio of base:**2b**:**1** and isolated as a yellow powder after trituration with ether, mp 153-154°. ir: 1695, 1520, 1348 cm^{-1}; ^{1}H nmr: δ 8.08 (m, 2H), 7.45 (m, 5H), 7.08 (d, 1H, J = 8.6), 3.88 (s, 2H), 3.59 (s, 3H); ^{13}C nmr: δ 167.0, 158.2, 155.1, 144.1, 134.0, 129.9, 128.5, 128.0, 124.8, 123.9, 121.4, 117.2, 102.8, 51.7, 25.7; ms: *m/z* 311 (M^{+}). *Anal.* Calcd. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.18; N, 4.50. Found: C, 65.69; H, 4.22; N, 4.46.

Methyl 6-Nitro-2-(2-chlorophenyl)-4*H*-1-benzopyran-3-carboxylate (**3c**). This compound (0.45 g, 52%) was prepared using a 24:3:1 mole ratio of base:**2c**:**1** and isolated as a white powder after flash chromatography on a 25-cm silica gel column using 5-20% ether in hexanes, mp 154.5-155.5°. ir: 1727, 1705, 1665, 1529, 1344 cm^{-1}; ^{1}H nmr: δ 8.12 (d, 1H, J = 2.6), 8.08 (dd, 1H, J = 8.8, 2.6), 7.47 (d, 1H, J = 7.9), 7.43-7.32 (complex, 3H), 7.06 (d, 1H, J = 8.8), 3.91 (s, 2H), 3.58 (s, 3H); ^{13}C nmr: δ 165.8, 156.2, 155.1, 144.2, 133.7, 133.0, 130.7, 130.3, 129.5, 126.6, 124.9, 124.0, 121.4, 117.2, 105.2, 51.9, 25.2; ms: *m/z* 345, 347 (M^{+}, M^{+}+2). *Anal.* Calcd. for $C_{17}H_{12}ClNO_5$: C, 59.04; H, 3.47; N, 4.05. Found: C, 59.23; H, 3.52; N, 4.06.

2-Methyl-6-nitro-3-(phenylsulfonyl)-4*H*-1-benzopyran (**3d**). This compound (0.56 g, 68%) was prepared using an 8:1:1 mole ratio of base:**2d**:**1** and isolated as a light yellow powder after trituration with 12:3:1 ether:chloroform:methanol, mp 172-174°. ir: 1655, 1525, 1345, 1295, 1150 cm^{-1}; ^{1}H nmr: δ 8,19 (d, 1H, J = 2.9), 8.06 (dd, 1H, J = 9.0, 2.9), 7.96 (dd, 2H, J = 7.5, 1.6), 7.76 (m, 1H), 7.68 (t, 2H, J = 7.5), 7.20 (d, 1H, J = 9.0), 3.74 (s, 2H), 2.42 (s, 3H); ^{13}C nmr: δ 157.5, 153.5, 143.7, 140.4, 133.8, 129.7, 126.8, 125.1, 124.0, 120.8, 117.1, 111.6, 24.2, 17.5; ms: *m/z* 331, 333 (M^{+}, M^{+}+2). *Anal.* Calcd. for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.93; N, 4.23. Found: C, 58.12; H, 3.97; N, 4.17.

6-Nitro-2-phenyl-3-(phenylsulfonyl)-4*H*-1-benzopyran (**3e**). This compound (0.79 g, 80%) was prepared using an 8:1:1 mole ratio of base:**2e**:**1** and isolated as a light yellow powder after trituration with 12:3:1 ether:chloroform:methanol, mp 196-197°. ir: 1660, 1525, 1346, 1320, 1152 cm^{-1}; ^{1}H nmr: δ 8.08 (s, 1H), 8.05 (d, 1H, J = 9.0), 7.58-7.45 (complex, 4H), 7.42-7.35 (complex, 6H), 7.01 (d, 1H, J = 9.0), 4.00 (s, 2H); ^{13}C nmr: δ 157.5, 154.2, 144.2, 140.2, 133.2, 131.5, 130.4, 124.4, 128.8, 127.9, 127.5, 124.8, 124.1, 120.3, 117.3, 114.7, 25.5; ms: *m/z* 393, 395 (M^{+}, M^{+}+2). *Anal.* Calcd. for $C_{21}H_{15}NO_5S$: C, 64.12; H, 3.82; N, 3.56. Found: C, 64.15; H, 3.83; N, 3.53.

2-Methyl-6-nitro-3-(diphenylphosphinoyl)-4*H*-1-benzopyran (**3f**). This compound (0.68 g, 70%) was prepared using an 8:1:1 mole ratio of base:**2f**:**1** and isolated as an off-white powder after trituration with ether, mp 239.5-240.5°. ir: 1652, 1516, 1340, 1194 cm^{-1}; ^{1}H nmr: δ 8.05 (dd, 1H, J = 9.0, 2.6), 7.81 (d, 1H, J = 2.6), 7.78-7.70 (complex, 4H), 7.59 (m, 2H), 7.56-7.49 (complex, 4H), 7.02 (d, 1H, J = 9.0), 3.18 (d, 2H, J = 4.8), 2.28 (dt, 3H, J = 1.6. 1.5); ^{13}C nmr: δ 160.1 (d, J = 20.2), 155.0, 143.7, 132.2, 131.6 (d, J = 9.2), 131.3, 128.9 (d, J = 12.2), 124.6, 123.9, 120.2 (d, J = 9.2), 116.9, 98.3 (d, J = 106.8), 27.0 (d, J = 9.9), 19.2; ms: *m/z* 391 (M^{+}). *Anal.* Calcd. for $C_{22}H_{18}NO_4P$: C, 67.52; H, 4.60; N, 3.58. Found: C, 67.61; H, 4.63; N, 3.54.

2-Methyl-6-nitro-3-(dimethoxyphosphoryl)-4*H*-1-benzopyran (**3g**). This compound (0.38 g, 50%) was prepared using a 24:3:1 mole ratio of base:**2g**:**1** and isolated as a light yellow powder following preparative thin layer chromatography using ether as the eluant, mp 102-103°. ir: 1661, 1520, 1337, 1244 cm^{-1}; ^{1}H nmr: δ 8.05 (dd, 1H, J = 9.0, 2.7), 7.99 (m, 1H), 7.01 (d, 1H, J = 9.0), 3.77 (d, 6H, J = 11.2), 3.54 (d, 2H, J = 5.1), 2.36 (dt, 3H, J = 2.6, 1.5); ^{13}C nmr: δ 160.0 (d, J = 28.2), 154.9, 143.8, 124.5, 123.8, 120.5 (d, J = 9.9), 116.9, 94.7 (d, J = 200.0), 52.3 (m), 25.1 (d, J = 6.9), 18.5; ms: *m/z* 268 (M^{+}-OCH_3). *Anal.* Calcd. for $C_{12}H_{14}NO_6P$: C, 48.16; H, 4.68; N, 4.68. Found: C, 48.29; H, 4.74; N, 4.60.

3-Cyano-6-nitro-2-phenyl-4*H*-1-benzopyran (**3h**). This compound (0.47 g, 67%) was prepared using an 8:1:1 mole ratio of base:**2h**:**1** and isolated as a light orange powder after trituration with ether, mp 163-164°. ir: 2204, 1643, 1524, 1344 cm^{-1}; ^{1}H nmr: δ 8.15 (dd, 1H, J = 9.0, 2.7), 8.10 (m, 1H), 7.86 (dd, 2H, J = 7.9, 1.5), 7.58-7.48 (complex, 3H), 7.20 (d, 1H, J = 9.0), 3.88 (s, 2H); ^{13}C nmr: δ 160.8, 154.3, 144.8, 131.6, 130.8, 128.7, 127.8, 124.6, 124.4, 118.8, 118.2, 117.8, 83.3. 26.6; ms: *m/z* 278 (M^{+}). *Anal.* Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.60; N, 10.07. Found: C, 69.02; H, 3.59; N, 10.10.

3-Benzoyl-6-nitro-2-phenyl-4*H*-1-benzopyran (**3i**). This compound (0.76 g, 85%) was prepared using a 24:3:1 mole ratio of base:**2i**:**1** and isolated as a light orange powder after trituration with ether, mp 186-188°. ir: 1648, 1630, 1525, 1348 cm^{-1}; ^{1}H nmr: δ 8.14 (dd, 1H, J = 8.9, 2.4), 8.13 (s, 1H), 7.64 (dd, 2H, J = 7.9, 1.0), 7.34 (dd, 2H, J = 7.7, 1.3), 7.29 (t, 1H, J = 7.5), 7.22-7.12 (complex, 6H), 3.96 (s, 2H); ^{13}C nmr: δ 196.6, 155.7, 154.9, 144.0, 137.1, 132.8, 132.5, 130.2, 129.2, 129.0, 128.1 (2C), 124.9, 123.9, 121.5, 117.2, 109.9, 27.2; ms: *m/z* 357 (M^{+}). *Anal.* Calcd. for $C_{22}H_{15}NO_4$: C, 73.95; H, 4.20; N, 3.92. Found: C, 74.03; H, 4.25; N, 3.84.

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