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Forced Brominative Deoxygenation Improves the One-Step Conversion of a Ketone to an Alkenyl Bromide

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Dedicated to Professor Wolfgang beck on the Occasion of his 65th Birthday

The brominative deoxygenation [2] reaction constitutes a convenient replacement of ketonic oxygen by bromine, as in the one-step preparation of a bromoalkene **8** from a ketone **4**. Given the synthetical importance [3] of such alkenyl bromides in general, it appears apt to use this previously unreported example for communicating useful methodical improvements that we discovered recently.

The preparation of 2,6-dimethylbenzonitrile (**2**) from the corresponding commercial bromide **1** is much more convenient than the previously [2, 4] employed Sandmeyer method. Ethylmagnesium iodide reacted with the nitrile **2** efficiently to produce the pure imine **3** that could be hydrolyzed in good yield solely with 2M aqueous HCl to give the known [5] ketone **4** albeit very slowly. In the crucial treatment [6] with 2,2,2-tribromo-2,2-dihydro-1,3,2-benzodioxaphosphole (**5**), **4** is a typically „difficult" ketone reacting rather sluggishly to the desired bromoalkenes (*E*, *Z*)-**8** along with a large proportion of the α-bromoketone **6a**. While **6a** and residual [6] **4** could be easily removed [2] by chromatography, their immoderate appearance means an annoying diminution of product **8**. This problem of oxidative bromination might be avoided [2] by the use of dibromomethyl methyl ether preformed from **5** and methyl formate; however, this reagent requires still higher temperatures, and its application to ketone **4** was abandoned as an indication of an unknown side reaction was obtained when the first traces of product **8** could be detected.

Two experiments under opposite conditions provided insights that led to a minimization of oxidative bromination with the reagent **5**. Monitoring the time-dependent conversions in a tightly stoppered NMR tube, we noticed that the α-bromoketone **6a** was formed first but diminished later during the appearance of (*E*,*Z*)-**8**. On the other hand, repetition in an open vessel with continuous flushing by argon produced **6a** almost exclusively. Therefore, the escape of gaseous hydrogen bromide is detrimental for the intended synthesis of **8**. Pursuing our earlier [6] suspicion of a reductive reformation [7] of the initial ketones, we observed that **6a** was also reduced to **4** with triphenylphosphine and 2 equivalents of conc. hydrobromic acid at room temperature; but no further conversion to **8** occurred at +90 °C. It was a logical consequence to reduce **6a** with 2-bromo-1,3,2-benzo-dioxaphosphole (**7**) in the presence of HBr at + 90 °C (see Experimental), establishing the conditions for the suspected equilibration with **4** and **5**. Indeed, **6a** was now quickly converted to **4** and the latter transformed into (*E*,*Z*)-**8** with a half-life time $t_{1/2}$ = 6 d. Therefore, a proper variant of brominative deoxygenation for an indisposed ketone like **4** consists in heating it with a 1,2-dichloroethane solution of reagent **5** in a closed vessel of sufficiently large volume.

Under such forcing conditions, the *E*/*Z* proportions of **8** approached the calculated [2, 8] ratio of ca. 73/27. The (*E*)-isomer was assigned by the ^3J(*trans*) coupling of its aromatic *ipso*-carbon atom with the olefinic proton (methyl-protons selectively decoupled); however, this coupling constant was considerably smaller than that reported [9] for sp^3-carbon. This assignment agrees fully with expectations for chemical shift sequences based on the γ- effect (^{13}C) and on magnetic anisotropy effects (^1H) of the roughly perpendicular aryl substituent, with a ^1H NMR shift difference of (*E*,*Z*)-**8** opposite to that of the (1-bromo-1-butenyl)benzenes [10]. Some steric strain by Br/CH_3-3 repulsion in (*Z*)-**8** is thought to be a reason for the significantly reduced CH-coupling constant ^1J = 154.3 Hz of the olefinic C-2 atom, as compared with 160.6 Hz for (*E*)-**8**.

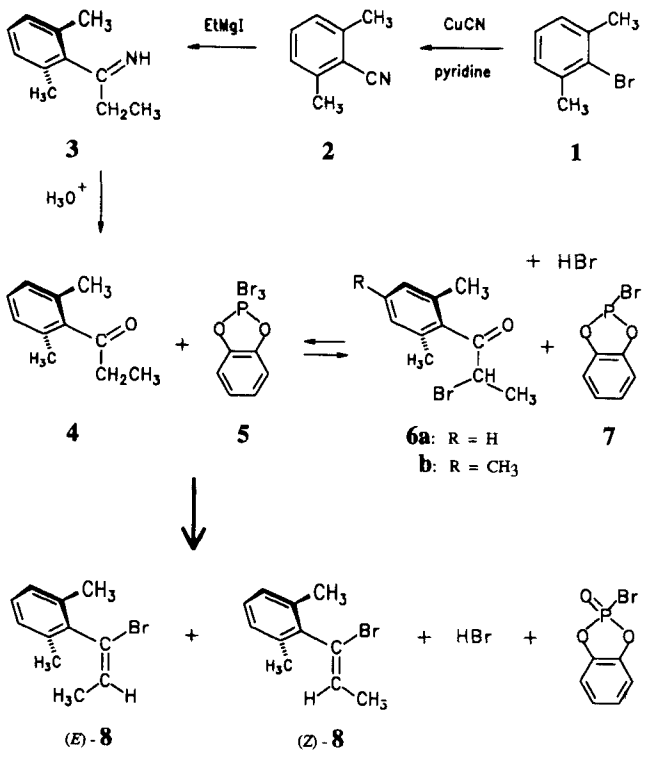
We are indebted to Mrs. Petra Böhrer for optimizing the new route [11] to nitrile **2**, and to the Deutsche Forschungsgemeinschaft for continuous support.

Experimental

IR: Bruker IFS-45. – ^1H NMR: Varian VXR-400S; Bruker WP-80-CW, AW-80-CW. – ^{13}C NMR: Varian VXR-400S; internal standard TMS; coupling constants (absolute magnitudes only) obtained by gated or selective decoupling, multiplicities by DEPT.

2,6-Dimethylbenzonitrile **2**

A 100-ml flask fitted with a long condenser was charged with commercial 2-bromo-1,3-dimethylbenzene (**1**, 10.0 g, 54.0



mmol), copper(I)-cyanide (15.0 g, 167 mmol), and pyridine (2.50 ml, 30.9 mmol). After heating to 180 °C under Ar for 17 h [11], practically all of the product **2** had sublimed into the condenser. This material (5.55 g, 78%) had *m.p.* 81–83 °C; ([4] 89–89.5 °C, [12] 89.7–90 °C) but was sufficiently pure (^{1}H NMR) for further use. The hard residue could be dissolved in a boiling mixture of ethane-1,2-diamine [13] (8 ml) and water (24 ml) to afford a small second crop of **2**.
^{1}H NMR (CCl_4): δ 2.51 (s, 2 CH_3), 7.04 and 7.23 (3 H, A_2B system).

1-(2,6-Dimethylphenyl)-1-propanimine **3**

The nitrile **2** (3.935 g, 30.0 mmol) dissolved in 20 ml of anhydrous xylene was added to a solution of 50 mmol of ethylmagnesium iodide in ether (26 ml). The ether was distilled off to maintain a reflux temperature of 125 °C for 3.5 h. After cautious hydrolysis, the contents were taken up in 50 ml of ether and 30 ml of 2N HCl and decanted from traces of residual magnesium metal. The separated organic layer was extracted with 2N HCl (3×20 ml). These aqueous extracts were combined, washed with ether (20 ml), alkalized with 5N NaOH, and shaken with ether (5×30 ml). The latter ethereal phases were combined, washed with water (50 ml), dried with $CaCl_2$, and concentrated to leave 4.18 g (86%) of colourless imine **3** with *m.p.* 49–50 °C. The analytical sample had *m.p.* 48–51 °C after distillation at 110–120 °C (bath temp.)/14 Torr.
IR (KBr): ν_{max} 3244 (sharp N–H), 2983, 2902, 1628, 1464, 1412, 1369, 1286, 1192, 922, 792 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ 1.21 (t, ^3J = 7.3 Hz, CH_3), 2.21 (s, 2 *o*-CH_3), 2.52 (q, ^3J = 7.3 Hz, CH_2), 7.02 and 7.10 (A_2B system, *m-/p*-H), ca. 8.4 (NH); in CCl_4 δ 1.17, 2.17, 2.43, 6.95. – ^{13}C NMR ($CDCl_3$): δ 9.4 (q, CH_3), 19.4 (q, 2 *o*-CH_3), 32.9 (t, CH_2), 127.60 (d, 2 *m*-C), 127.63 (d, *p*-C), 132.9 (s, 2 *o*-C), 142.7 (s, *ipso*-C), 184.9 (s, CN).

$C_{11}H_{15}N$	Calcd.	C 81.94	H 9.37	N 8.69
(161.2)	Found	C 82.19	H 9.52	N 8.69

1-(2,6-Dimethylphenyl)-1-propanone **4**

The reaction of nitrile **2** (3.00 g, 22.9 mmol) in 25 ml of anhydrous xylene with ethylmagnesium iodide (36.6 mmol in 30 ml of ether) was conducted as described for **3**, including the extraction into 2N HCl (70 ml). This solution of **3**-hydrochloride was washed with ether (30 ml) and refluxed for 5 d at 125 °C bath temperature. After extraction of **4** into ether (50 ml and 3×15 ml), the combined extracts contained some iodine and were decolourized with aqueous $NaHSO_3$ (37%, 2×15 ml), washed with water, dried with $MgSO_4$, and concentrated. The brown residue (2.68 g, 72%) was distilled to give **4** as a pale yellow oil with *b.p.* 109–114 °C/15 Torr ([5] 120.6–121 °C/21 Torr).
^{1}H NMR (CCl_4): δ 1.14 (t, ^3J = 7.2 Hz, CH_3), 2.15 (s, 2 *o*-CH3), 2.59 (q, ^3J = 7.2 Hz, CH_2), 6.85 and 6.98 (A_2B system, *m-/p*-H).
The acidic aqueous phase yielded 330 mg (9%) of residual imine **3** after workup as described there.

2-Bromo-1-(2,6-dimethylphenyl)-1-propanone **6a**

The ^{1}H NMR spectral data of this material were sufficiently similar to those of the known [14] *p*-methyl derivative **6b** such that further characterization was deemed unnecessary. – ^{1}H NMR (CCl_4): δ 1.85 (d, ^3J = 6.6 Hz, CH_3), 2.26 (s, 2 *o*-CH_3), 4.70 (q, ^3J = 6.6 Hz, CHBr), 6.91 and 7.08 (A_2B system, *m-/p*-H).

2-(1-Bromo-1-propenyl)-1,3-dimethylbenzene 8
General Procedure [2] (Variant) for indisposed ketones

A dry round-bottomed flask (250 ml) was charged with 2-bromo-1,3,2-benzodioxaphosphole (**7**, 1.58 ml, 12.5 mmol), 5.0 ml of dry 1,2-dichloroethane, and a magnetic stirring bar under inert gas, then cooled in an ice bath. After dropwise addition of bromine (0.58 ml, 11.3 mmol) with stirring, the developing reagent **5** was kept at room temperature for 15 min. and recooled in ice for introduction of the ketone **4** (1.62 g, 10.0 mmol). The flask was closed with a gas-tight stopper, secured by a spring of medium tension, and heated at +90 °C for 6.5 days behind a safety shield. A slight underpressure was noticed on opening the flask at room temperature. The contents were cooled in ice, diluted with 25 ml of pentane, and stirred for 15 min after the addition of aqueous 2N NaOH (30 ml). The aqueous layer was shaken with more pentane (2 ×25 ml), and the combined pentane layers were washed with 2N NaOH (3×25 ml) and water (25 ml), then dried with $CaCl_2$ and concentrated. The residue (2.12 g) consisted of (*E*)-**8**, (*Z*)-**8**, **6a** and **4** in a 46:30:19:5 ratio. It was separated at silica gel (20 g, 100–200 µm) by chromatography with low-boiling petroleum ether (190 ml) to afford 1.45 g (64%) of a liquid mixture of (*E*)-**8** (42%) and (*Z*)-**8** (22%). – IR (film): ν_{max} 3065, 3019, 2918, 2854, 1466, 847, 771, 716 cm^{-1}. – Further elution (240 ml) with petroleum ether containing 10% of ether gave 0.56 g (27%) of a mixture of **6a** (16%) and reformed [6] ketone **4** (11%).

(*E*)-**8**. – ^{1}H NMR ($CDCl_3$): δ 1.39 (d, ^3J = 7.0 Hz, CH_3), 2.28 (s, 2 *o*-CH_3), 6.28 (q, ^3J = 7.0 Hz, CH), 7.04 and 7.12 (A_2B system, *m*-/*p*-H). – ^{13}C NMR ($CDCl_3$): δ 15.5 (qd, ^1J = 128 Hz, ^2J = 2.8 Hz, CH_3), 19.4 (qd, ^1J = 127 Hz, ^3J = 4.8 Hz, 2 *o*-CH_3), 119.4 (pseudo-qui, $^3J \approx {}^2J$ = 7.6 Hz, C–Br), 127.5 (dm, ^1J = 159 Hz, 2 *m*-C), 128.4 (d, ^1J = 59.3, *p*-C), 129.6 (dq, ^1J = 160.6 Hz, ^2J = 6.9 Hz, C-2), 136.2 (dq, ^3J = 7.5, ^2J = 6.4 Hz, 2 *o*-C), 137.1 (qm, ^3J = 7.3 Hz on methyl-proton decoupling, *ipso*-C).

(*Z*)-**8**. – ^{1}H NMR ($CDCl_3$): δ 1.92 (d, ^3J = 6.4 Hz, CH_3), 2.28 (s, 2 *o*-CH_3), 5.78 (q, ^3J = 6.4 Hz, CH), 7.02 and 7.10 (A_2B system, *m*-/*p*-H). – ^{13}C NMR ($CDCl_3$): δ 17.3 (qd, ^1J = 128 Hz, ^2J = 2.8 Hz, CH_3), 19.8 (qd, ^1J = 127 Hz, ^3J = 4.8 Hz, 2 *o*-CH_3), 123.3 (pseudo-qui, $^3J \approx {}^2J$ = 8.6 Hz, C–Br), 127.4 (dm, ^1J = 159 Hz, 2 *m*-C), 127.7 (dq, ^1J = 154.3 Hz, ^2J = 6.9 Hz, C-2), 128.2 (d, ^1J = 159.3, *p*-C), 136.7 (dq, ^3J = 7.5 , ^2J = 6.6 Hz, 2 *o*-C), 140.4 (unresolved m on methyl-proton decoupling, *ipso*-C).

$C_{11}H_{13}Br$	Calcd.	C 58.69	H 5.82
(225.1)	Found.	C 59.26	H 5.94

Recycling of **6a** to **4** and (*E*,*Z*)-**8**: The pure α-bromoketone 6a (980 mg, 4.06 mmol) was diluted with 3 ml of dry 1,2-dichloroethane in a 100-ml flask under Ar and cooled in an ice bath. 2-Bromo-1,3,2-benzodioxaphosphole (**7**) was added in a such an amount (1.139 ml, 1.971 g, 9.00 mmol) that a part of it could convert all of the water (3.9 mmol) subsequently introduced as conc. (48%) hydrobromic acid (0.090 ml) into HBr (calcd. total 4.7 mmol). On further treatment as above for **8**, the α-bromoketone was quickly consumed but 50% of ketone **4** were still present after 6 d ($t_{1/2}$) at +90 °C, isolated in admixture (654 mg) with (*E*)-**8** (25%) and (*Z*)-**8** (10%). – After 12 d at +90 °C, the product ratio was ca. 25:60:15.

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