Cleavage of *tert*-Butyl Benzoates with NaH in DMF: Comments on the Mechanism and a Simple and Safe Alternative Procedure

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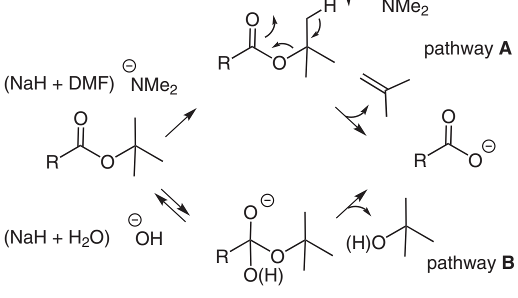
Abstract: The hazardous and inconvenient Schmidt procedure for *tert*-butyl benzoate ester cleavage by NaH in DMF has been reinvestigated. The reaction is suggested to involve $B_{AC}2$ ester cleavage, facilitated by adventitious, NaH-derived NaOH, rather than the proposed E2 elimination of isobutylene by DMF-derived $NaNMe_2$. Powdered KOH in THF is a significantly safer and simpler alternative that effects cleavage of *tert*-butyl benozoates, at ambient temperature, in excellent yield (94–99%).

Key words: *tert*-butyl esters, cleavage, hydrides, DMF, hazard

The hindered nature of the *tert*-butyl group, and the relative stability of the *tert*-butyl carbocation, engender *tert*-butyl esters with useful properties as protecting groups for carboxylic acids; a feature that has been extensively exploited.[1] There are numerous methods for cleavage of *tert*-butyl esters to reveal the corresponding carboxylic acid. However, nearly all of them involve Brønsted or Lewis acidic catalysts or reagents.[1]

In 2002, Schmidt reported a 'new base-mediated method for the cleavage of *tert*-butyl esters'[2] that proceeded in 60–87% yield by use of NaH (8 equiv) in DMF (25–80 °C, 2–24 h).[2,3] An E2 mechanism for the cleavage was proposed,[2] in which $NaNMe_2$,[3] generated in situ from the NaH and DMF,[3,4] acts as the base, thus generating the corresponding sodium carboxylate and isobutylene (Scheme 1, pathway A).



Scheme 1 Cleavage of *tert*-butyl esters to generate the corresponding sodium carboxylate under the conditions reported by Schmidt,[2] together with the mechanism (pathway A) that was proposed. Also shown is an alternative pathway (B) based on subsequent observations (see text for full details) which may also involve deprotonation of $[RC(OH)(O)t\text{-}Bu]^-$ by a further equivalent of NaOH: see parentheses around protons.

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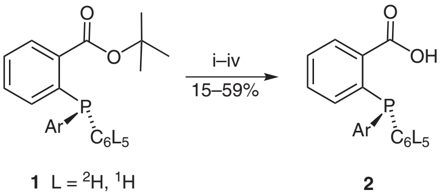
In the context of the development of a synthesis of enantiomerically enriched $^2H_5$-labelled *o*-diarylphosphino benzoic acids (Scheme 2) we needed a method for *tert*-butyl benzoate cleavage (**1** → **2**).[5] Key requirements were that the reaction must involve nonacidic conditions, in order to avoid any potential for H–D exchange in the C_6D_5 moiety, and proceed at ambient temperature, to avoid racemisation of the thermally labile P-stereogenic centres. Use of the Schmidt procedure[2] [NaH, DMF (i–iv), Scheme 2] appeared promising in this regard, but test reactions gave poor results: proceeding very slowly, giving **2** in poor yields (15–59%) and often containing numerous side products. The reactions also became progressively worse as we attempted to scale-up for the preparation of synthetically useful quantities.



Scheme 2 Inefficient cleavage of *tert*-butyl *o*-diarylphosphino benzoates **1** by NaH and DMF.[2] *Reagents and conditions*: (i) NaH (8 equiv), DMF, 22 °C, 48.5 h; (ii) DMF removed in vacuo; (iii) residue quenched with H_2O; (iv) acidified to pH 1 with HCl.

In view of the potential hazards of this reaction,[4] as well as the tedious workup involving evaporation of the DMF and then cautious quenching of the NaH-laden residue with water,[2] we abandoned this method. Nonetheless, we had noticed a number of features during this early phase of investigation that led us to question the mechanistic proposal of Schmidt[2,3] (pathway A, Scheme 1). Crucially, *tert*-butanol was detected (^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopy) in the reaction mixture after workup. Moreover, when the DMF (Aldrich, anhydrous grade) was further dried (3 Å MS) prior to addition of **1a** (Ar = Ph, L = ^1H) and NaH, the *tert*-butyl ester cleavage essentially ceased after four hours – with only 16.5% conversion of **1a** – according to $^{31}P\{^1H\}$ NMR analysis (Figure 1). On stepwise addition of substoichiometric quantities of water (100–300 μL, 5 M solution H_2O in DMF), *tert*-butyl ester cleavage proceeded smoothly, but in a stepwise manner. Taken together, these results suggested to us that under the conditions employed by Schmidt,[2] traces of water, present in DMF, react with the NaH to generate anhydrous NaOH.[6,7]

Analysis of the stoichiometry of water added versus **1a** converted (Figure 1) yielded a ratio of ca. nine, similar in value to the eight equivalents of NaH employed by Schmidt[2] for full conversion. The stoichiometry may relate to precipitation of NaOH (as aggregates or complexes with carboxylate) from the reaction medium.[7]

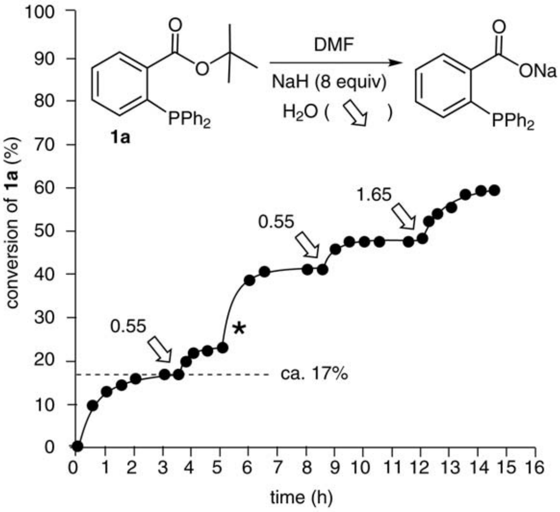


Figure 1 Effect of addition of aliquots of water on the conversion (y-axis) of **1a** to the sodium salt of **2a** according to $^{31}P\{^1H\}$ NMR analysis of reaction samples (4% vol.). Line through data points is drawn solely as an aid to the eye. *Reagents and conditions*: $[\mathbf{1a}]_0 = 0.1$ M in DMF (Aldrich, 'anhydrous', dried over 3 Å MS for 15 d), NaH (8 equiv), Ph_3P (internal NMR standard) and H_2O (5 M in DMF; added in portions). The asterisk indicates entry of adventitious water during sampling.

It should be noted that under the published conditions,[2] even 99% pure DMF can contain sufficient water to achieve complete hydrolysis of the eight equivalents of NaH. The NaOH thus generated can effect a $B_{AC}2$-type[8] cleavage of the ester (Scheme 1, pathway B), possibly via deprotonation of the intermediate to give a dianion.[9] Cleavage via a $B_{AC}n$, not $B_{AL}n$, ($n = 1, 2$), process (cf. pathway B) was confirmed by reaction of alkyl-[$^{18}O_{0.48}$] *tert*-butyl benzoate (**3a**) with NaH and H_2O in DMF-d_7 which yielded [$^{18}O_{0.47}$]-*tert*-butanol (Figure 2).

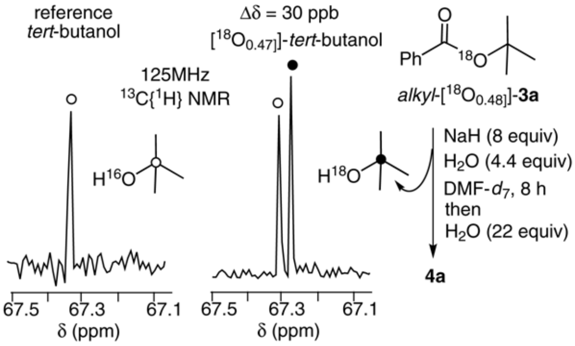


Figure 2 Subspectrum from $^{13}C\{^1H\}$ NMR analysis of the reaction of alkyl-[$^{18}O_{0.48}$] *tert*-butyl benzoate with NaH (8 equiv) and H_2O (4.4 equiv) in DMF-d_7 for 8 h (ca. 40% conversion).

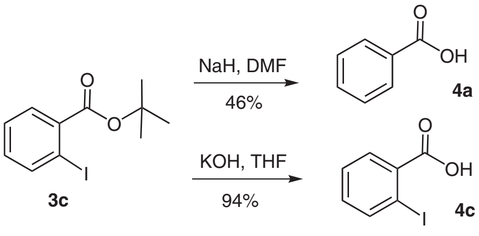
Table 1 Comparison of Yield of Benzoic Acids (2-ArXCO$_2$H, **2ab** and **4a–c**) Obtained after Workup, for the Cleavage of *tert*-Butyl Esters (2-ArXCO$_2$*t*-Bu, **1ab** and **3a–c**) Using NaH in DMF[2] versus KOH in THF

Entry	2-ArXCO$_2$*t*-Bu; X =	Yield[a] (Time)	
		NaH in DMF[b,c]	KOH in THF[c,d]
1	P(Ph)$_2$ (**1a**)	18–55% (–)[e]	97% (24 h)
2	P(C$_6$D$_5$)(*p*-BrC$_6$H$_4$) (**1b**)	15–59% (–)[e]	97% (17 h)
3	H (**3a**)	61% (48 h)	98% (6 h)
4	Me (**3b**)	71% (48 h)[f]	97% (30 h)
5	I (**3c**)	0% (48 h)[g]	94% (3 h)

[a] Yield refers to that of carboxylic acid 2-ArXCO$_2$H (**2ab**, **4a–c**), after purification by column chromatography or crystallisation.
[b] Reaction conditions as (i–iv) Scheme 2.
[c] Degassed solvent used with **1a** and **1b** to avoid phosphine oxidation.
[d] Reaction conducted with laboratory-grade THF, 0.1 M ester (0.02 M for **1a**), 8 equiv of freshly powdered KOH, at ambient temperature, followed by acidification to pH 1 with 12 M HCl and extractive workup.
[e] Compounds **2a** and **2b** obtained from NaH in DMF are impure, and the yields are based on a range of experiments (reaction times 18–117 h) and are estimated by $^{31}P\{^1H\}$ NMR analysis with a weighed Ph_3P standard.
[f] Reported in ref. 2 as 74% in 6 h.
[g] Benzoic acid (**4a**) isolated in 46% yield.

Anhydrous hydroxides in aprotic polar media have significantly greater nucleophilicity than they do in hydrous or protic media.[10] Indeed, in Pedersen's pioneering work on crown ethers, *tert*-butyl benzoate esters were cleaved using KOH and 18-crown-6 in toluene at 100 °C,[11] whilst Gassman reported the same cleavage with two equivalents of H_2O and eight equivalents KO*t*-Bu in diethyl ether at ambient temperature.[9] However, simply by using powdered KOH[12] in laboratory grade THF, there is no requirement for 18-crown-6,[10] or KO*t*-Bu.[9] Under these conditions, the benzoate **1a** was cleaved efficiently at ambient temperature to give **2a** in 97% isolated yield (Table 1, entry 1).[13] A small range of other *tert*-butyl benzoates (**1b** and **3a–c**) were also tested and gave similar results (entries 2–5). In all cases the reactions yielded the carboxylic acid in high purity, in contrast to cleavage conducted under the NaH and DMF conditions[2] where side products were often evident. This is particularly evident for the *o*-iodobenzoate (**3c**, entry 5) where a competing NaH-mediated deiodination[14,15] affords benzoic acid (**4a**, 46%) with NaH and DMF (Scheme 3). In contrast, reaction is complete in just three hours with KOH and THF to afford *o*-iodobenzoic acid (**4c**) in 94% yield.

In summary, using dry DMF, we were unable to efficiently cleave *tert*-butyl *o*-diphenylphosphino benzoate **1a** using the NaH in DMF mediated general procedure reported by Schmidt.[2] The effect of deliberate addition of small quantities of wet DMF to generate anhydrous NaOH in



Scheme 3 Contrasting outcomes from cleavage of *tert*-butyl ester **3c** with NaH in DMF[2] and KOH in THF.[13] Acids **4a** and **4c** are obtained after acidic workup.

situ (Figure 1) together with co-generation of *tert*-butanol through $B_{AC}2$-type cleavage (Scheme 1, pathway B), weigh against the proposed[2] $NaNMe_2$-mediated E2 process (pathway A). Since NaH can undergo uncontrollable exothermic reaction with DMF, particularly at scale, and with onset temperatures as low as 26 °C when the DMF is not dry,[4] the NaH in DMF method[2] is potentially very hazardous.[16] KOH in THF was found to be an operationally simpler and much safer alternative procedure for the cleavage of *tert*-butyl benzoates under basic conditions, affording the corresponding benzoic acids in high yields (Table 1).

Acknowledgment

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References and Notes

(1) See, for example: (a) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, **2003**. (b) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley and Sons: New Jersey, **2007**.

(2) Paul, S.; Schmidt, R. R. *Synlett* **2002**, 1107.

(3) The reaction of DMF with NaH has been reported to generate $NaNMe_2$ and either an equimolar mixture of H_2 and CO, or formaldehyde: (a) Nasipuri, D.; Bhattacharya, A.; Hazra, B. G. *J. Chem. Soc. D* **1971**, 660. (b) Powers, J. C.; Seidner, R.; Parsons, T. G. *Tetrahedron Lett.* **1965**, *6*, 1713.

(4) Mixtures of NaH and DMF can undergo uncontrollable exothermic decomposition at temperatures as low as 26 °C, with higher onset temperatures in very dry solvent. In some cases these exothermic reactions have resulted in violent eruptions of the mixture from the reaction vessel, in particular when conducted at scale. See: Bretherick, L. *Handbook of Reactive Chemical Hazards*, 4th ed.; Butterworth-Heinemann: Oxford, **1990**, 1181; and references therein.

(5) For the synthesis of unlabelled parent compound **2a**, see: Hoots, J. E.; Rauchfuss, T. B.; Wrobleski, D. A. *Inorg. Synth.* **1982**, *21*, 175.

(6) Serrano-Wu, M. H.; Regueiro-Ren, A.; St. Laurent, D. R.; Carroll, T. M.; Balabsubramanian, B. N. *Tetrahedron Lett.* **2001**, *42*, 8593.

(7) Reaction of **3b** and powdered NaOH in DMF proceeded to 74% conversion (to **4b**) over a period of 6 d. The generation of NaOH in situ (by NaH and H_2O) may lead to a much more reactive (nonaggregated) form of NaOH, possibly metastable. Alternatively, NaH may mediate deprotonation of the tetrahedral intermediate in pathway **B**. *tert*-Butyl ester cleavage of **1a** (0.2 M) employing $NHEt_2$ and NaH in anhydrous THF proceeded to 45% conversion (to **4b**) over a period of 4 d.

(8) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, **1987**, 718–719.

(9) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918.

(10) Roberts, W.; Whiting, M. C. *J. Chem. Soc.* **1965**, 1290.

(11) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.

(12) NaOH in DMF was less effective, see ref. 7. For reactions in THF, replacement of KOH by NaOH or LiOH led to a significant reduction in yield of **2a** from **1a**. Reduction in the formal number of equivalents of KOH results in a reduction of reaction rate. Increasing to 16 equiv of KOH resulted in quantitative conversion of **3a** to **4a** in <2 h.These effects may relate to the surface area of the KOH exposed to the THF medium.

(13) **Typical Experimental Procedure for Ester Cleavage**
tert-Butyl *o*-iodobenzoate (**3c**, 304 mg, 1.00 mmol, 1 equiv) was dissolved in THF (10 mL), and then ground KOH (449 mg, 8.00 mmol, 8 equiv) added. The resulting suspension was stirred at r.t. for 3 h, after which TLC analysis [hexane–EtOAc (20:1), R_f(**3c**) = 0.54] indicated complete reaction. After addition of H_2O (10 mL) and washing the resulting aqueous solution with EtOAc (10 mL), the solution was acidified to pH 1, resulting in precipitation. The aqueous suspension was extracted with EtOAc (3 × 10 mL) and the extracts combined, dried ($MgSO_4$), filtered, and the volatiles removed in vacuo to yield **4c** as a white amorphous solid, 232 mg (94%); Mp 160–161 °C (lit.[17] 162 °C). ^{1}H NMR [300 MHz, $(CD_3)_2SO$, TMS]: $\delta = 7.24$ [ddd, $^{3}J(^{1}H,^{1}H) = 7.9$ Hz, $^{3}J(^{1}H,^{1}H) = 7.4$ Hz, $^{4}J(^{1}H,^{1}H) = 1.7$ Hz, 1 H, H(4)], 7.48 [ddd, $^{3}J(^{1}H,^{1}H) = 7.7$ Hz, $^{3}J(^{1}H,^{1}H) = 7.4$ Hz, $^{4}J(^{1}H,^{1}H) = 1.2$ Hz, 1 H, H(5)], 7.71 [ddd, $^{3}J(^{1}H,^{1}H) = 7.7$ Hz, $^{4}J(^{1}H,^{1}H) = 1.7$ Hz, $^{5}J(^{1}H,^{1}H) = 0.5$ Hz, 1 H, H(6)], 7.99 [ddd, $^{3}J(^{1}H,^{1}H) = 7.9$ Hz, $^{4}J(^{1}H,^{1}H) = 1.2$ Hz, $^{5}J(^{1}H,^{1}H) = 0.5$ Hz, 1 H, H(3)], 13.29 (br s, 1 H, CO_2H).[18]

(14) **Typical Experimental Procedure for Ester Cleavage with Loss of Iodide**
Compound **3c** (152 mg, 0.50 mmol, 1 equiv) was dissolved in DMF (5 mL), followed by the addition of NaH (60% w/w in mineral oil, 96 mg, 4.00 mmol, 8 equiv) resulting in gas evolution. The resulting suspension was stirred at r.t. for 48 h. After cooling to 0 °C, the remaining NaH was quenched by the careful addition of H_2O (10 mL), and the resulting aqueous solution was washed with EtOAc (10 mL). The solution was acidified to pH 1, resulting in product precipitation, and the aqueous suspension was extracted into EtOAc (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and the volatiles removed in vacuo to yield crude **4a** as a yellow oil. This was applied to a presolvated silica gel column (1.5 × 11 cm) and eluted with 7:1 PE (40:60 fraction)–EtOAc, collecting 5 mL fractions. Fractions 7–15 were combined and the volatiles removed in vacuo to give **4a** as a white amorphous solid, 28 mg (46%); mp 114–118 °C (lit.[19] 122 °C). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 7.48$ [m, 2 H, H(3,5)], 7.62 [m, 1 H, H(4)], 8.13 [m, 2 H, H(2,6)], 11.42 (br s, 1 H, CO_2H).[18]

(15) For the reduction of ArI to ArH by NaH in THF, see: (a) Nelson, R. B.; Gribble, G. W. *J. Org. Chem.* **1974**, *39*, 1425. (b) For the reduction of methyl *o*-iodobenzoate by NaOMe, MeOH, with radiation ($\lambda = 350$ nm), to methyl benzoate, see: Kashimura, T.; Kudo, K.; Mori, S.; Sugita, N. *Chem. Lett.* **1986**, 851.

(16) Whilst we did not experience any uncontrollable reactions of NaH with the DMF (up to scales of ca. 10 mL DMF, 0.19 g NaH, at 21 °C), there are ample literature reports (see ref. [4])

and anecdotal evidence of such occurrences. These strongly support the conclusion that the procedure in Scheme 2 is potentially very hazardous.

(17) (a) Furniss, B. S.; Handford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: London, **1989**. (b) Krasnokutskaya, E. A.; Semenischeva, N. I.; Filimonov, V. D.; Knochel, P. *Synthesis* **2007**, 81.

(18) Spectroscopic data were identical to those obtained from commercially available samples (Aldrich) of **4a** and **4c**.

(19) *Concise Chemical and Technical Dictionary*, 1st ed.; Bennett, H., Ed.; Chemical Publishing Co.: New York, **1947**, 107.