A Convenient Procedure for Parallel Ester Hydrolysis

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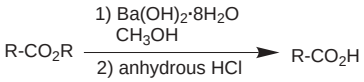
Abstract: The treatment of alkyl esters with barium hydroxide octahydrate in methanol followed by protonation with anhydrous hydrogen chloride affords carboxylic acids. The procedure does not require aqueous workup and is particularly suitable for parallel synthesis applications.

Key words: ester hydrolysis, deprotection, parallel synthesis, barium hydroxide octahydrate, 9-chloroacridine

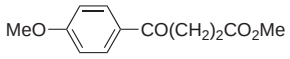
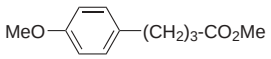
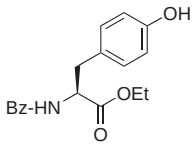
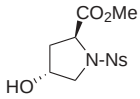
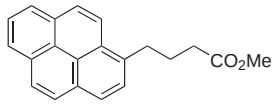
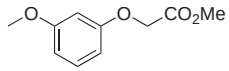
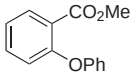
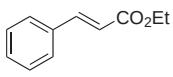
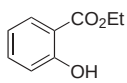
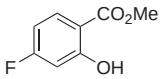
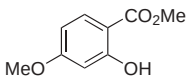
Esters are commonly used protecting groups in multi-step organic synthesis. Deprotection is often carried out using acidic or basic hydrolysis conditions in various aqueous solvent systems (e.g. THF–MeOH–H_2O). Conventional methods almost always include an aqueous workup step, which is difficult to implement in the parallel synthesis of libraries. Non-hydrolytic methods of ester-cleavage have been reported, including BCl_3,[1] BBr_3,[2] and NaI/pyridine.[3] However, these conditions are often non-selective, causing reaction with non-ester functional groups (e.g. aryl alkoxides). To provide a general and selective method for hydrolysis of esters that is useful in parallel synthesis, we examined non-aqueous conditions of hydroxide-mediated ester cleavage. Barium hydroxide octahydrate, which is soluble in methanol, has been previously used to deprotect simple alkyl esters.[4] A non-aqueous workup was devised for the reagent where the products are concentrated, protonated using anhydrous hydrogen chloride, dried over $MgSO_4$, and isolated by filtration (Equation 1). These operations are easily implemented in parallel.



Equation 1 Ester hydrolysis followed by non-aqueous protonation with anhydrous hydrogen chloride

To explore the generality of the method, several model reactions were conducted (Table 1). Entries 1–4 proceeded in varying times at room temperature, while entries 5–11 required heating. Entry 5 required a small amount of THF as a co-solvent. In all cases, product was obtained in good to quantitative yield.

Table 1 Examples of Ester Hydrolysis Using Barium Hydroxide Octahydrate Followed by Non-Aqueous Workup (Bz = benzoyl; Ns = 2-nitrobenzenesulfonyl)

Entry	Substrate	Isolated yield (%)	Conditions
1		85	2 h, r.t.
2		98	2 h, r.t.
3		87	15 h, r.t.
4		93	15 h, r.t.
5		100	4 h, 80 °C, MeOH–THF (6:1)
6		80	2 h, 80 °C
7		97	2 h, 80 °C
8		100	2 h, 80 °C
9		87	2 h, 80 °C
10		100	2 h, 80 °C
11		94	2 h, 80 °C

The procedure was also utilized in a typical parallel synthesis route: a solution-phase, three-step, one-pot route to 9-chloroacridines without purification of intermediates (Equation 2). Thus aryl triflates (**1**), readily available from the corresponding salicylic acids, were coupled with anilines (**2**) using Buchwald's conditions.[5] The crude ester product was then hydrolyzed with barium hydroxide octahydrate in methanol, followed by treatment with phosphorous oxychloride[6] to yield 9-chloroacridines (**3**).

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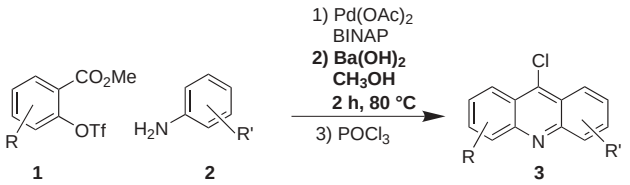
In this case the crude barium carboxylate salts were utilized directly in the cyclization step, omitting an explicit protonation step. The 9-chloroacridine products were purified automatically by SiO_2 chromatography using the CombiFlash® system (Isco™). The sequence was evaluated for a series of substrates (Table 2). Entries 1–7 show the generation of purified products in reasonable yields and excellent purity. In the case of entry 8, the coupling reaction was successful, but ester hydrolysis did not proceed to completion, even after several days in refluxing methanol. This may be due to deactivation caused by the two electron-donating groups in the molecule. However, the method is reliable with a single strong electron-donating group (entries 1–5).

In summary, a method has been described for performing ester hydrolysis reactions which avoids aqueous workup.[7] The reaction is particularly useful in parallel synthesis applications where such workups are impractical. The method appears to be fairly general allowing hydrolysis of both alkyl and aryl esters.



Equation 2 Three-step synthesis of 9-chloroacridines avoiding aqueous workup

Acknowledgment

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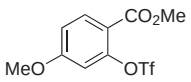
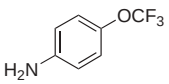
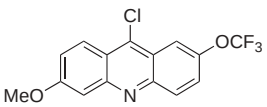
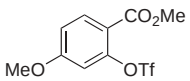
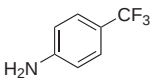
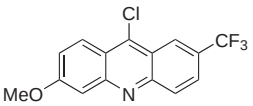
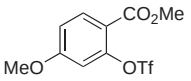
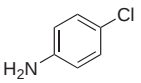
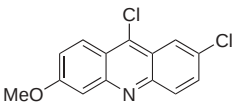
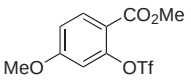
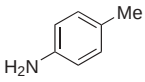
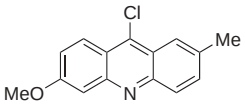
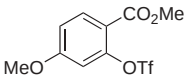
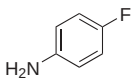
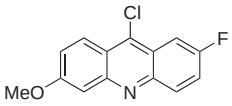
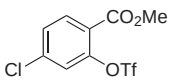
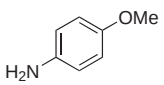
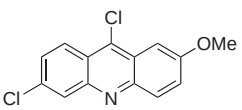
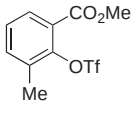
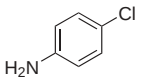
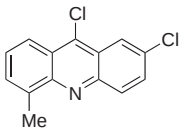
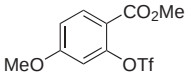
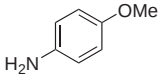
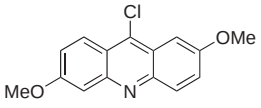
Table 2 Examples of Parallel 9-Chloroacridine Synthesis

Entry	Salicyl triflate	Aniline	Product	^{1}H NMR (400 MHz, $CDCl_3$)	Isolated yield, % (purity, %)[a]
1				δ = 4.01 (s, 3 H), 7.34 (dd, 1 H, *J* = 2.2, 9.5 Hz), 7.43 (s, 1 H), 7.64 (d, 1 H, *J* = 9.5 Hz), 8.17–8.20 (m, 2 H), 8.29 (d, 1 H, *J* = 9.2 Hz)	50 (99)
2				δ = 4.04 (s, 3 H), 7.37 (dd, 1 H, *J* = 2.6, 9.5 Hz), 7.45 (d, 1 H, *J* = 2.6 Hz), 7.92 (dd, 1 H, *J* = 1.8, 9.2 Hz), 8.25 (d, 1 H, *J* = 9.2 Hz), 8.34 (d, 1 H, *J* = 9.5 Hz), 8.73 (s, 1 H)	45 (99)
3				δ = 4.02 (s, 3 H), 7.33 (dd, 1 H, *J* = 2.6, 9.5 Hz), 7.42 (d, 1 H, *J* = 2.6 Hz), 7.71 (dd, 1 H, *J* = 2.6, 9.2 Hz), 8.08 (d, 1 H, *J* = 9.2 Hz), 8.29 (d, 1 H, *J* = 9.2 Hz), 8.38 (d, 1 H, *J* = 2.2 Hz)	47 (98)
4				δ = 2.62 (s, 3 H), 4.01 (s, 3 H), 7.30 (dd, 1 H, *J* = 2.6, 9.5 Hz), 7.43 (d, 1 H, *J* = 2.6 Hz), 7.63 (dd, 1 H, *J* = 1.8, 8.8 Hz), 8.05 (d, 1 H, *J* = 8.8 Hz), 8.14 (s, 1 H), 8.30 (d, 1 H, *J* = 9.2 Hz)	40 (100)
5				δ = 4.01 (s, 3 H), 7.32 (dd, 1 H, *J* = 2.6, 9.5 Hz), 7.41 (d, 1 H, *J* = 2.2 Hz), 7.58 (t, 1 H, *J* = 9.5 Hz), 7.99 (dd, 1 H, *J* = 2.6, 9.5 Hz), 8.14 (dd, 1 H, *J* = 5.5, 9.5 Hz), 8.27 (d, 1 H, *J* = 9.5 Hz)	44 (100)
6				δ = 4.04 (s, 3 H), 7.50–7.52 (mult, 2 H), 7.55 (d, 1 H, *J* = 9.2), 8.08 (d, 1 H, *J* = 10), 8.19 (s, 1 H), 8.33 (d, 1 H, J = 9.2)	48 (99)
7				δ = 2.78 (s, 3 H), 7.22 (t, 1 H, *J* = 7.8 Hz), 7.32 (d, 1 H, *J* = 7.8 Hz), 7.68 (dd, 1 H, *J* = 3.0, 8.8 Hz), 7.86–7.90 (m, 2 H), 8.27 (d, 1 H, *J* = 2.9 Hz)	33 (95)
8				n/a	No reaction during ester hydrolysis

[a] Purity gauged by RP-HPLC analysis (UV detection at 254 nm).

References

(1) Manchand, P. S. *J. Chem. Soc., Chem. Commun.* **1971**, *13*, 667.
(2) Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427.
(3) Magnus, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 389.
(4) For example: (a) Inoue, K.; Sakai, K. *Tetrahedron Lett.* **1977**, *46*, 4063. (b) Bascop, S.-L.; Laronze, J.-Y.; Sapi, J. *Synthesis* **2002**, 1689. (c) Papot, S.; Rivault, F.; Tranoy, I.; Gesson, J.-P. *Synlett* **2002**, 164.
(5) Ahman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363.
(6) (a) Maxime, R.; Faure, R.; Perichaud, A.; Galy, J.-P. *Synth. Commun.* **2002**, *32*, 981. (b) Lormier, A. T.; Boyer, G.; Gaure, R.; Galy, J. P. *Heterocycles* **2002**, *57(3)*, 449. (c) Cain, B. F.; Atwell, G. J. *J. Med. Chem.* **1976**, *19*, 1408. (d) Acheson, R. M.; Harvey, C. W. C. *J. Chem. Soc., Perkin Trans. 1* **1976**, 465.
(7) **Typical Procedure**: A solution of ethyl salicylate (0.161 g, 0.968 mmol) in MeOH (10 mL) was treated with $BaOH{\cdot}8H_2O$ (0.458 g, 1.45 mmol, 1.5 equiv) and heated to 80 °C for 2 h. Solvent was removed in vacuo, followed by the addition of HCl (1 M in Et_2O) (10 mL) and $MgSO_4$, and the mixture was filtered, and concentrated to afford salicylic acid (0.115 g, 87%).