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Practical cleavage of trifluoroacetamides with *p*-toluensulfonic acid

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ABSTRACT

A practical and efficient cleavage of trifluoroacetamides with *p*-TsOH·H_2O has been developed. The deprotected amines are isolated directly from the reaction mixture as tosylate salts. This method can be applied to both secondary and tertiary trifluoroacetamides in good isolated yields.

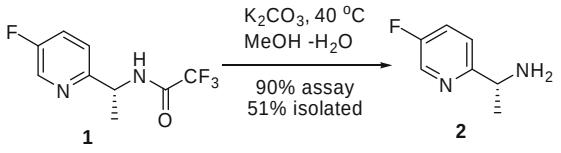
The trifluoroacetamide group is synthetically useful in the protection of primary and secondary amines due to its ease of introduction and, more importantly, easy cleavage.[1,2] The most commonly used cleavage method involves basic hydrolysis in aqueous MeOH using bases such as K_2CO_3 or Na_2CO_3, NH_3 or $Ba(OH)_2$.[3–9]

Under these reaction conditions, the isolation of the amine products requires an extractive workup, which is typically followed by solvent switches or concentrations. This isolation work greatly reduces the efficiency of an otherwise extremely simple reaction. Moreover, the resulting amines may have significantly high solubility in water, making it very difficult to recover the desired product from the aqueous washes.

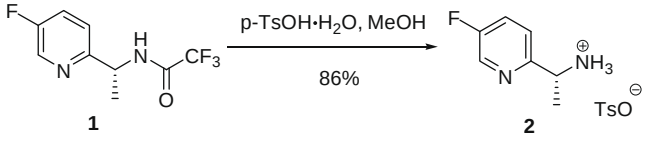
We recently encountered this problem in the preparation of amine **2** from trifluoroacetamide **1** (Scheme 1). Although the deprotection reaction takes place in 90% yield at 40 °C using K_2CO_3 as the base, extracting the free amine from the aqueous layer during the reaction workup proved extremely difficult, resulting in almost 40% loss in yield in the aqueous layers.

In order to design a more efficient process for this reaction, we decided to attempt an acidic non-aqueous deprotection of trifluoroacetamide **1**.[10] Hydrochloric acid in methanol had been used previously[11] to promote this reaction. However, handling and use of HCl at multi-kilogram scale require safety measures such as use of scrubbers to scavenge acidic vapors. In order to avoid handling and exposure to HCl vapors, we decided to look for an alternative acid for this chemistry.

We were glad to find that refluxing a methanol solution of trifluoroacetamide **1** with 1 equiv of *p*-toluenesulfonic acid for 24 h cleanly afforded amine **2** as a tosylate salt (Scheme 2). This salt can be directly isolated from the reaction mixture by crystallization upon addition of MTBE as weak solvent. This procedure avoids aqueous conditions and workup, and the direct isolation of the tosylate salt makes the process highly efficient. The deprotection of



Scheme 1.



Scheme 2.

trifluoroacetamide **1** under these conditions takes place in 86% isolated yield.

We have examined the generality of this deprotection method for other heterocycle containing trifluoroacetamides. We felt that these substrates would have a higher tendency to be water soluble and thus more prone to isolation problems under base-catalyzed deprotection conditions. The results are summarized in Tables 1 and 2. All the substrates examined afforded upon deprotection crystalline tosylate salts that could be recovered in high yield by crystallization from the reaction mixture after addition of an appropriate weak solvent.

Deprotection of aminomethyl pyridines (Table 1, entries 1 and 2) is slow and required over 48 h of reflux in MeOH. By contrast, cleavage of aminopyridines (Table 1, entries 3–6) is fast, requiring only 2–3 h of reflux in MeOH. Deprotection of tertiary trifluoroacetamides[12] was uniformly fast. All reactions were complete after 2–3 h of refluxing in MeOH (Table 2, entries 1–4). We found that the isolation of secondary amine tosylate salts was best performed from an *i*PrOH/*i*PrOAc solvent system. This required performing a solvent switch from MeOH to *i*PrOH after reaction completion,

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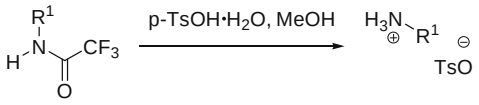
Table 1
p-TsOH·H_2O deprotection of secondary trifluoroacetamides[13,14]



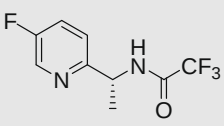
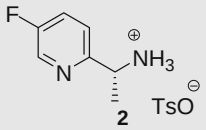
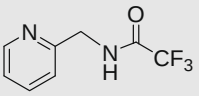
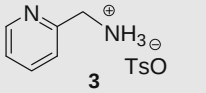
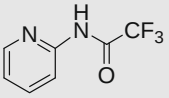
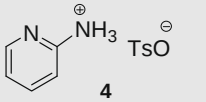
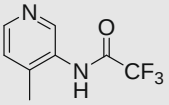
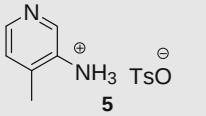
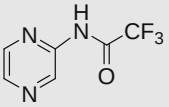
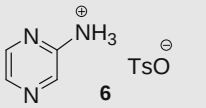
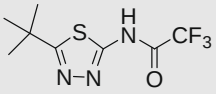
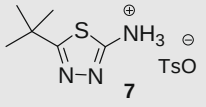
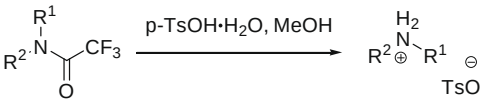
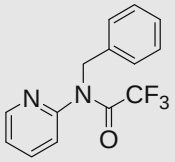
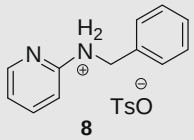
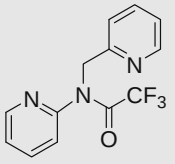
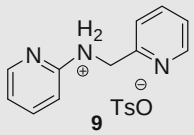
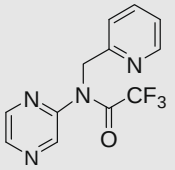
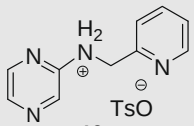
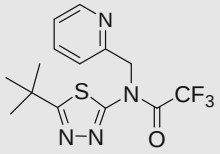
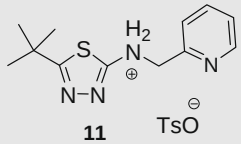
Entry	Starting material	Product	Isolated yield (%)
1		 **2**	86
2		 **3**	96
3		 **4**	99
4		 **5**	86
5		 **6**	94
6		 **7**	92

Table 2
p-TsOH·H_2O deprotection of tertiary trifluoroacetamides[13,14]



Entry	Starting material	Product	Isolated yield (%)
1		 **8**	81
2		 **9**	87
3		 **10**	77
4		 **11**	88

followed by the addition of *i*PrOAc to crystallize the desired products in 77–88% yield.

In summary, a practical non-aqueous cleavage of trifluoroacetamides with *p*-TsOH·H_2O in methanol has been developed to afford tosylate salts that can be isolated directly from the reaction mixture. By avoiding an aqueous workup, the reactions are much more efficient and amenable to large scale work. This method can be applied to both secondary and tertiary trifluoroacetamides with good isolated yields.

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13. *Typical deprotection procedure*: Trifluoroacetamide **1** was dissolved in MeOH (5 mL/g trifluoroacetamide). *p*-TsOH·H_2O (1 equiv) was added and the resulting solution was heated to ~65 °C and aged at that temperature until HPLC or TLC showed complete reaction. The reaction mixture was then cooled to 20 °C, and MTBE (10 mL/g trifluoroacetamide) was added over 1 h. The slurry was aged for 1 h at 20 °C, then cooled to 5 °C, and held for 1 h. The solids were filtered, washed with MTBE, and dried under vacuum at 20 °C. Yield of **2** was 86%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (d, J = 6.8 Hz, 3H), 2.28 (s, 3H), 4.56 (q, J = 6.8 Hz, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.60 (dd, J_1 = 4.4 Hz, J_2 = 8.7 Hz, 1H), 7.81 (td, J_1 = 3.0 Hz, J_2 = 8.7 Hz, 1H), 8.34 (b, 3H), 8.60 (d, J = 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.3, 21.1, 50.2, 123.7 (d, J = 10 Hz), 124.8 (d, J = 20 Hz), 125.9, 128.5, 137.3 d, J = 30 Hz), 138.3, 145.6, 154.2 (d, J = 10 Hz), 159.2 (d, J = 250 Hz).
14. All compounds isolated gave consistent ^{1}H NMR, ^{13}C NMR, and GCMS or LCMS data. **3**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.29 (s, 3H), 4.20–4.23 (d, J = 5.6 Hz, 2H), 7.13–7.11 (d, J = 7.9 Hz, 2H), 7.43–7.52 (m, 4H), 7.88–7.92 (dt, J = 7.7 Hz, J = 1.6 Hz, 1H), 8.29 (b, 3H), 8.63–8.64 (d, J = 4.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.76, 42.56, 122.72, 123.53, 125.47, 128.07, 137.63, 137.74, 145.45, 148.58, 152.91.
Compound **4**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.28 (s, 3H), 6.82–6.85 (dt, J_1 = 7.1 Hz, J_2 = 1 Hz, 1H), 7.01–7.03 (d, J = 9.0, 1H), 7.14–7.16 (d, J = 8.0 Hz, 2H), 7.57–7.56 (d, J = 8.0 Hz, 2H), 7.89–7.93 (m, 2H), 8.09 (b, 2H), 13.43 (b, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.77, 112.13, 113.50, 125.47, 128.31, 135.84, 138.36, 144.11, 144.63, 153.99.
Compound **5**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.28 (s, 6H), 6.30 (b, 2H), 7.14–7.12 (d, J = 8.0 Hz, 2H), 7.53–7.55 (dd, J_1 = 6.6 Hz, J_2 = 1.5 Hz, 2H), 7.59–7.58 (d, J = 5.7 Hz, 1H), 7.97–7.95 (d, J = 5.7 Hz, 1 Hz), 8.04 (s, 1H), 14.81 (b, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 18.26, 21.26, 124.54, 125.98, 127.84 128.22, 128.69, 138.52, 140.23, 145.64, 146.92.
Compound **6**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.29 (s, 3H), 7.13–7.11 (dd, J_1 = 10.4 Hz, J_2 = 0.9 Hz, 2H), 7.47–7.50 (dd, J_1 = 10.1 Hz, J_2 = 2.1 Hz, 2H), 7.81–7.82 (d, J = 4.2 Hz, 1H), 7.92–7.93 (dd, J_1 = 3.4 Hz, J_2 = 1.3 Hz, 1H), 8.18–8.19 (d, J = 1.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 2.74, 125.45, 128.18, 129.18, 132.48, 137.42, 138.07, 144.94, 150.76.
Compound **7**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.33 (s, 9H), 2.29 (s, 3H), 7.13–7.14 (d, J = 7.7 Hz, 2H), 7.52–7.50 (d, J = 8.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.75, 29.40, 36.06, 125.47, 128.14, 137.97, 145.11, 167.85, 169.51.
Compound **8**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.28 (s, 3H), 5.45 (s, 2H), 6.95–6.98 (dt, J_1 = 6.9 Hz, J_2 = 1.1 Hz, 1H), 7.13–7.10 (m, 3H), 7.25–7.23 (d, J = 7.1 Hz, 2H), 7.43–7.37 (m, 3H), 7.49–7.48 (d, J = 8.0 Hz, 2H), 7.94–7.91 (dt, J_1 = 8.5 Hz, J_2 = 1.2 Hz, 1H), 8.16–8.15 (d, J = 6.1 Hz, 1H), 8.49 (b, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.72, 55.08, 113.22, 115.26, 125.44, 127.28, 128.00, 128.38, 128.92, 133.28, 137.56, 140.05, 142.62, 145.69, 153.98.

Compound **9**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.31 (s, 3H), 5.61 (s, 2H), 6.64–6.62 (t, J_1 = 6.8 Hz, J_2 = 6.2 Hz, 1H), 7.08–7.10 (d, J = 8 Hz, 2H), 7.24–7.26 (m, 1H), 7.50–7.42 (m, 2H), 7.73–7.67 (m, 4H), 7.93–7.92 (d, J = 6.7 Hz, 1H), 8.45–8.44 (d, J = 4.9 Hz, 1H), 8.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.40, 57.29, 113.19, 116.73, 124.37, 124.81, 126.03, 128.97, 139.17, 139.98, 140.25, 141.90, 142.84, 148.40, 151.36, 155.26.
Compound **10**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.29 (s, 3H), 5.58 (s, 2H), 7.12–7.10 (d, J = 7.7 Hz, 2H), 7.38–7.40 (dt, J_1 = 7.2 Hz, J_2 = 2 Hz, 1H), 7.47–7.49 (d, J = 8.1 Hz, 2H), 7.55–7.57 (d, J = 7.8 Hz, 1H), 7.88–7.91 (dt, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 8.02–8.02 (d, J = 4.3 Hz, 1H), 8.09–8.10 (d, J = 4.2 Hz, 1H), 8.49–8.50 (d, J = 4.7 Hz, 1H), 8.65 (s, 1H), 9.23 (b, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.72, 56.13, 122.97, 123.54, 125.42, 128.03, 130.06, 131.26, 137.35, 137.65, 142.78, 145.53, 148.48, 149.26, 151.24.
Compound **11**: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.31 (s, 9H), 2.29 (s, 3H), 5.56 (s, 2H), 7.11–7.12 (d, J = 7.8 Hz, 2H), 7.38–7.40 (dd, J = 1.8 Hz, J = 7.7 Hz, 1H), 7.45–7.49 (m, 3H), 7.86–7.90 (dd, J = 1.8 Hz, J = 7.7Hz, 1H), 8.54–8.55 (d, J = 3.4 Hz, 1 H), 9.99 (b, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 20.73, 29.10, 36.23, 53.89, 122.14, 123.40, 125.44, 128.02, 137.33, 137.64, 145.55, 149.30, 152.64, 166.53, 168.18.