Application of 2,2,2-Trichloroethoxycarbonyl Protection to Aminoacridines

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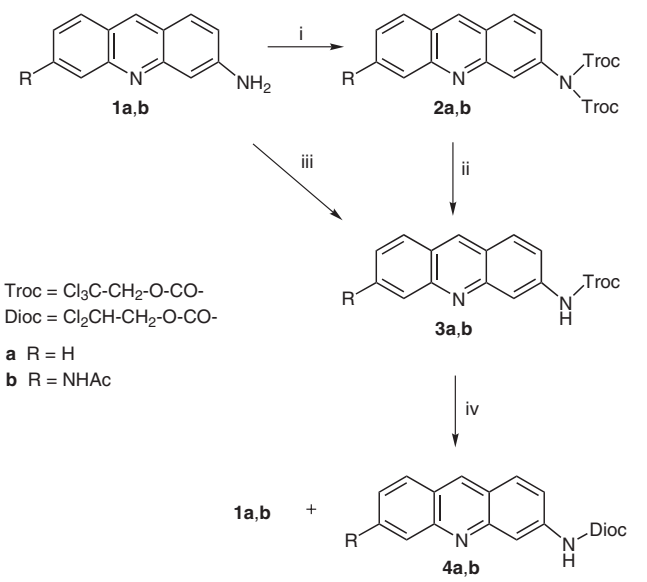
Abstract: The 2,2,2-trichloroethoxycarbonyl (Troc) group has been successfully used as a protecting group for aminoacridines. Unlike aliphatic amines, deprotection of these aromatic amines yields significant amounts (12–29%) of stable 2,2-dichloroethoxycarbonyl (Dioc) by-products. Formation of bis-carbamates, through the introduction of butoxycarbonyl (Boc) moieties as temporary protecting groups, efficiently solves this problem.

Key words: fused-ring systems, heterocycles, amino protecting group, carbamate

In the course of a program committed to the synthesis of antitumor agents, we have been developing and extending the chemistry of 3,6-diaminoacridine (proflavine).[1] The key step in the sequence of reactions leading to the cytotoxic 4-hydroxymethyl-3-amino acridine derivatives, is the selective protection of one amino group of proflavine. The protecting group has to be stable towards the harshly acidic conditions (methanesulfonic acid, concentrated hydrochloric acid or trifluoroacetic acid) required for further functionalization of the acridine nucleus but must also be labile under other, mild conditions due to the high reactivity of the final molecules. Since these conditions preclude the use of amido (i.e. acetamido, benzamido) or phthalimido groups, methylsulfonamide was first chosen as a protecting group. Unfortunately, this group could not be removed effectively under the mild conditions required. In an alternative approach, we investigated the use of the carbamate functionality, since this group was also considered to be capable of fulfilling the requirements. Indeed, the ethoxycarbonyl group was successfully introduced, however, all attempts at its removal, without decomposition of other parts of the molecule, failed. Other carbamate groups such as *N*-allyloxycarbonyl (Alloc) and 9-fluorenylmethyloxycarbonyl (Fmoc) were also considered, however, removal of the former was found to decompose the highly sensitive dihydro[1,3]oxazino intermediate, whilst the latter could only be prepared in moderate yield and the resulting protected molecule was only sparingly soluble in water or most organic solvents. Finally, the 2,2,2-trichloroethoxycarbonyl (Troc) group seemed suitable to achieve our goals.

Troc protection is frequently used in organic synthesis, especially in syntheses of aminosugars,[2–11] because it is orthogonal to many other amino protecting groups.[12] Most conditions for Troc removal described in the literature involve a reductive elimination process. Originally, Troc was cleaved by zinc in aqueous acetic acid,[13] but several modifications have since been reported. Other reagents have also been described, including indium in aqueous methanol,[14] cadmium in acetic acid–dimethylformamide,[2] cadmium–lead alloy in acetic acid,[3] and electrolysis.[15] Most authors have focused on the chemoselectivity of the deprotection methodology and, in most cases, the final amines could be easily purified by column chromatography. In our case, however, purification of the resulting aminoacridine derivatives constituted a real challenge due to the high polarity and low solubility of the deprotected molecules. It was therefore critical to design a methodology that allowed both quantitative deprotection and easy isolation of the final products. It is worth mentioning that Troc protection has not previously been applied to amines attached to nitrogen heterocycles, and we could anticipate some differences in reactivity compared to aliphatic amines. We describe, in this paper, the use of the Troc group to protect aminoacridines, with the 3-amino- and the 3-acetylamino-6-aminoacridines **1a** and **1b**, chosen as model compounds with which to optimize the protection/deprotection reactions.

Due to the lower reactivity of aminoacridines compared to simple aliphatic or aromatic amines, introduction of Troc



Scheme 1 *Reagents and conditions*: i) TrocCl, py, r.t.; ii) py, 60 °C; iii) TrocCl, py, 0 °C; iv) Zn in AcOH, or Cd in DMF–AcOH, or Cd/Pb (10%) in THF–$AcONH_4$.

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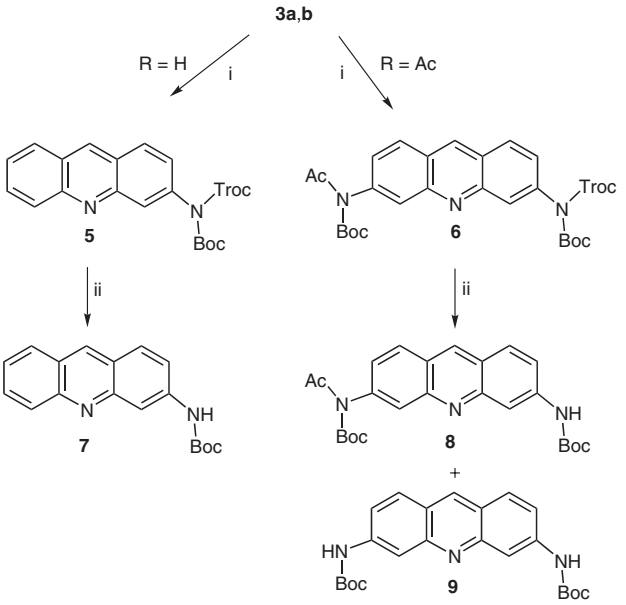
required the use of a large excess of reagent (TrocCl) in pyridine (Scheme 1). Nevertheless, the reaction proceeded smoothly at room temperature under the conditions used to introduce the ethoxycarbonyl group onto aminoacridines.[1] Unlike previous observations, the reaction quantitatively yielded the N,N-diprotected compounds **2a** and **2b**. Heating the reaction mixture at 60 °C, slowly but quantitatively converted these diprotected derivatives into their monoprotected counterparts **3a** and **3b**. However, monoprotection could also be directly achieved, in good yields (77–93%), by careful control of both temperature (0 °C) and reaction time (the course of reaction was followed by HPLC).

In order to study the deprotection step, we applied the most efficient deprotection conditions reported in the literature that were also compatible with the presence of the acridine heterocycle. The reactions were monitored by HPLC and reaction products were isolated and identified by both NMR and mass spectrometry. The results are collected in Table 1. As shown in Scheme 1, each of the three conditions investigated led to the isolation of two compounds in addition to unreacted starting material (**3a** or **3b**): the desired deprotected compounds **1a** or **1b** and a less polar compound that was later identified as the dichloroethoxycarbonylamino (Dioc) derivative **4a** or **4b**. Though several authors have previously mentioned monodechlorination of the Troc group under reductive conditions, the resulting dichloroethoxycarbonyl compounds were never fully characterized and this side-reaction was therefore never quantified. Dioc-substituted compounds **4a** and **4b** exhibit characteristic NMR signals: a doublet arising from the CH_2 at $\delta = 6.64$ ppm and a triplet for the CH at $\delta = 6.56$–6.58 ppm. As indicated in Table 1, significant amounts (12–29%) of side-products **4a** and **4b** were formed. Though the use of a Cd/Pb mixture generated larger amounts of Dioc derivatives **4a** and **4b** (entries 3 and 7) than other methods of deprotection, in both cases, the workup and isolation of the desired compounds were found to be easier. These conditions were therefore used to perform the reactions on larger scales for isolation and full characterization of the reaction products.

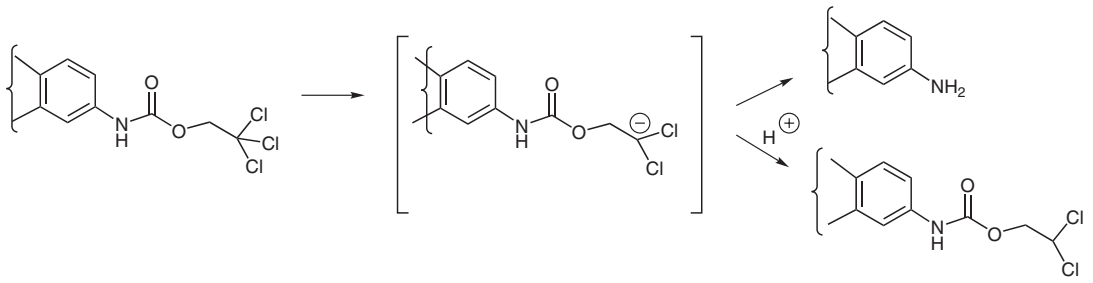
The formation of the stable Dioc derivatives from Troc-protected amines could be explained by the quenching of the intermediate anions by protons (Scheme 2).[15]

We hypothesized that formation of the Dioc derivatives may be favored by the highly acidic character of the NH-Troc hydrogen of **3a** and **3b**, reinforced by the delocalization of the exocyclic amine electron pair onto the acridine nucleus. To investigate this hypothesis, we introduced a second protecting group onto the carbamate function (Scheme 3).



Scheme 3 *Reagents and conditions*: i) Boc_2O, py; ii) Cd/Pb (10%), THF–$AcONH_4$ (pH 7).

We chose the Boc group, since this is orthogonal to Troc (Scheme 3) and, taking advantage of the acidic character of NH-Troc, it was introduced under basic conditions (pyridine) in good yields [92% and 77% (not optimized) respectively for **5** and **6**]. Deprotection of Troc could then be achieved using the conditions described above (Cd/Pb in pH 7 buffered solution). As indicated in Table 1, Troc removal was almost quantitative, with the Boc-protected aminoacridine **7** isolated in 98% yield from **5**. In the case of diamine **6**, in addition to the major compound **8**, we also observed a partial elimination of the acetyl group with formation of **9** in 8% yield. In both cases, the presence of Boc greatly facilitated isolation and purification by chromatography by considerably lowering the polarity of the Troc-deprotected products. The Boc group could be easily and quantitatively removed under a range of standard conditions (TFA or AcOH/HCl).



Scheme 2

Table 1 Comparative Yields and Reaction Conditions[a]

	Compound	Conditions	Reaction time (min)	Deprotected compound (%)[b]	Side-product (%)[b]
1	**3a**	**A**	90	**1a** (86)	**4a** (14)
2	**3a**	**B**	90	**1a** (88)	**4a** (12)
3	**3a**	**C**	60	**1a** (84)	**4a** (16)
4	**5**	**C**	90	**7** (98)	–[c]
5	**3b**	**A**	90	**1b** (87)	**4b** (13)
6	**3b**	**B**	90	**1b** (82)	**4b** (18)
7	**3b**	**C**	30	**1b** (71)	**4b** (29)
8	**6**	**C**	60	**8** (92), **9** (8)	–[c]

[a] **A**: Zn (120 equiv), AcOH; **B**: Cd (100 equiv), DMF, AcOH; **C**: Cd/Pb 10%[3] (15 equiv), THF, $AcONH_4$ (pH 7).
[b] The yields were calculated from the NMR data by integration of the singlet corresponding to the highly sensitive H-9 proton.
[c] Not detected.

In conclusion, the use of Troc as a protecting group for aminoacridines is an interesting alternative to the Boc or ethoxycarbonyl protection methods previously described. However, the formation of dichloroethoxycarbonyl (Dioc) derivatives as side-products during deprotection is an important limitation considering the purification problems associated with aminoacridines. The introduction of a temporary protecting group (Boc) on the same nitrogen effectively solves this problem and allows all three steps (Boc introduction, Troc deprotection and Boc deprotection) to be achieved in high yields. It is likely that this methodology could be generalized and applied to other amino-substituted heterocycles.

Melting points were obtained on a Reichert Thermovar instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer with DMSO as internal standard. Mass spectra were recorded on a Polarisq Thermo Finnigan spectrometer. Elemental analyses were performed at 'Service de microanalyse, Université Joseph Fourier'. All starting materials are commercially available.

Troc Protection; General Procedure

TrocCl (11.25 mmol) was added dropwise to a solution of aminoacridine **1a**,**b** (1.4 mmol) in pyridine (20 mL) cooled to 0 °C. When all the starting material had been consumed, the solvent was evaporated and the resulting oil was stirred in aq NH_4OH (50 mL, pH 10) and the resulting precipitate was filtered, washed with H_2O (3 × 50 mL). The product was purified by chromatography on silica gel (**3a**; EtOAc, 100%) or by recrystallization (**3b**; 2-propanol).

3-(2,2,2-Trichloroethoxycarbonyl)aminoacridine (3a)

Yellow solid; yield: 93%; mp 140–142 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.65 (s, 1 H, NH), 8.99 (s, 1 H, H-9), 8.37 (s, 1 H, H-4), 8.14–8.07 (m, 3 H, H-8, H-1, H-5), 7.84–7.72 (m, 2 H, H-7 or H-6, H-2), 7.58–7.53 (m, 1 H, H-7 or H-6), 5.04 (s, 2 H, CH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.2, 149.6, 149.2, 140.5, 136.2, 130.9, 129.7, 129.0, 128.8, 125.8, 125.5, 123.5, 120.8, 113.9, 96.1, 74.0.

Anal. Calcd for $C_{16}H_{11}Cl_3N_2O_2$: C, 52.00; H, 3.00; N, 7.58. Found: C, 52.30; H, 3.07; N, 7.51.

3-Acetamido-6-(2,2,2-trichloroethoxycarbonyl)aminoacridine (3b)

Brown solid; yield: 77%; mp 234–238 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.60 (s, 1 H, NHTroc), 10.34 (s, 1 H, NHAc), 8.86 (s, 1 H, H-9), 8.49 (s, 1 H, H-4), 8.29 (s, 1 H, H-5), 8.08–8.02 (m, 2 H, H-8, H-1), 7.68 (dd, *J* = 9, 1.8 Hz, 1 H, H-7), 7.61 (dd, *J* = 9, 1.7 Hz, 1 H, H-2), 5.04 (s, 2 H, CH_2), 2.16 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.0, 151.8, 149.8, 149.5, 140.8, 140.1, 135.2, 129.3, 129.1, 122.4, 122.3, 120.1, 119.4, 113.8, 113.4, 95.8, 73.6, 24.2.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{14}Cl_3N_3O_3$: 426.0174 (^{35}Cl); found: 426.0174 (^{35}Cl).

3-(2,2-Dichloroethoxycarbonyl)aminoacridine (4a)

Yellow solid; yield: 16%; mp 124–128 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.48 (s, 1 H, NH), 8.99 (s, 1 H, H-9), 8.35 (s, 1 H, H-4), 8.13–8.07 (m, 3 H, H-8, H-1, H-5), 7.84–7.79 (m, 1 H, H-7 or H-6), 7.71 (dd, *J* = 9.1, 2.0 Hz, 1 H, H-2), 7.59–7.53 (m, 1 H, H-7 or H-6), 6.58 (t, *J* = 5.2 Hz, 1 H, $CHCl_2$), 4.64 (d, *J* = 5.2 Hz, 2 H, CH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.9, 149.7, 149.3, 140.8, 136.2, 130.9, 129.7, 129.0, 128.9, 125.8, 125.4, 123.4, 120.8, 113.6, 70.6, 68.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{16}H_{12}Cl_2N_2O_2$: 335.0349 (^{35}Cl); found: 335.0349 (^{35}Cl).

3-Acetamido-6-(2,2-dichloroethoxycarbonyl)aminoacridine (4b)

Yellow solid; yield: 29%; mp 179–182 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.42 (s, 1 H, NHTroc), 10.33 (s, 1 H, NHAc), 8.84 (s, 1 H, H-9), 8.48 (s, 1 H, H-4), 8.26 (s, 1 H, H-5), 8.06–8.01 (m, 2 H, H-8, H-1), 7.66–7.59 (m, 2 H, H-7, H-2), 6.56 (t, *J* = 5.2 Hz, 1 H, $CHCl_2$), 4.63 (d, *J* = 5.2 Hz, 2 H, CH_2), 2.16 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.5, 152.8, 150.2, 150.0, 141.1, 140.7, 135.6, 129.7, 129.5, 122.8, 122.6, 120.5, 119.9, 114.2, 113.5, 70.6, 68.6, 24.7.

Anal. Calcd for $C_{21}H_{19}Cl_3N_2O_4 \cdot 0.25\ H_2O$: C, 54.49; H, 3.94; N, 10.59. Found: C, 54.56; H, 4.11; N, 10.55.

Introduction of the Boc Group; General Procedure

Boc_2O (0.31 mmol) was added to a solution of **3a**,**b** (0.13 mmol) in pyridine (5 mL) and the solution was stirred at r.t. overnight. The solvent was then evaporated under reduced pressure and the oily residue was stirred in aq NH_4OH (10 mL, pH 10). The resulting precipitate was filtered and washed with H_2O (3 × 10 mL).

3-[*N*-*tert*-Butoxycarbonyl-*N*-(2,2,2-trichloroethoxycarbonyl)]aminoacridine (5)

Light yellow solid; yield: 92%; mp 154–156 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.17 (s, 1 H, H-9), 8.24–8.15 (m, 3 H, H-5, H-1, H-8), 8.08 (s, 1 H, H-4), 7.90–7.86 (m, 1 H, H-7 or H-6), 7.68–7.63 (m, 1 H, H-7 or H-6), 7.56 (dd, *J* = 8.9, 1.8 Hz, 1 H, H-2), 4.94 (s, 2 H, CH_2), 1.40 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 150.7, 150.5, 149.1, 148.6, 139.9, 136.6, 131.3, 129.4, 129.2, 129.0, 127.6, 127.0, 126.7, 126.6, 125.5, 95.1, 84.1, 75.1, 27.8.

Anal. Calcd for $C_{21}H_{19}Cl_3N_2O_4$: C, 53.70; H, 4.08; N, 5.97. Found: C, 53.35; H, 4.18; N, 6.02.

3-(*N*-Acetyl-*N*-*tert*-butoxycarbonyl)amino-6-[*N*-*tert*-butoxycarbonyl-*N*-(2,2,2-trichloroethoxycarbonyl)]aminoacridine (6)

Beige solid; yield: 77%; mp 100–105 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.20 (s, 1 H, H-9), 8.25–8.18 (m, 2 H, H-8, H-1), 8.09 (s, 1 H, H-4), 7.95 (s, 1 H, H-5), 7.58 (dd, *J* = 8.9, 1.7 Hz, 1 H, H-7), 7.46 (dd, *J* = 8.9, 1.6 Hz, 1 H, H-2), 4.94 (s, 2 H, CH_2), 2.58 (s, 3 H, CH_3), 1.40–1.35 (m, 18 H, 2 × *t*-Bu).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.7, 152.2, 150.6, 150.5, 149.1, 148.8, 141.5, 140.1, 136.6, 129.5, 129.2, 128.1, 127.8, 127.5, 127.3, 125.7, 125.6, 95.1, 84.1, 83.5, 75.1, 27.9, 26.7.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{28}H_{30}Cl_3N_3O_7$: 626.1222 (^{35}Cl); found: 626.1222 (^{35}Cl).

3-*tert*-Butoxycarbonylaminoacridine (7)

Yellow solid; yield: 98%; mp 181–182 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.84 (s, 1 H, NH), 8.93 (s, 1 H, H-9), 8.30 (s, 1 H, H-4), 8.11–8.04 (m, 3 H, H-5, H-1, H-8), 7.81–7.77 (m, 1 H, H-7 or H-6), 7.68 (dd, *J* = 9.1, 1.6 Hz, 1 H, H-2), 7.66–7.50 (m, 1 H, H-7 or H-6), 1.54 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 153.1, 149.9, 149.2, 141.6, 135.9, 130.7, 128.9, 128.8, 125.6, 125.1, 123.2, 121.0, 112.8, 80.1, 28.5.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{18}N_2O_2$: 295.1428; found: 295.1433.

3-(*N*-Acetyl-*N*-*tert*-butoxycarbonyl)amino-6-*tert*-butoxycarbonylaminoacridine (8)

Yellow solid; yield: 92%; mp 182–185 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.88 (s, 1 H, NHBoc), 8.97 (s, 1 H, H-9), 8.31 (s, 1 H, H-4), 8.12–8.05 (m, 2 H, H-8, H-1), 7.83 (s, 1 H, H-5), 7.63 (d, *J* = 9.0 Hz, 1 H, H-7), 7.31 (d, *J* = 8.8 Hz, 1 H, H-2), 2.57 (s, 3 H, CH_3), 1.55 (s, 9 H, *t*-Bu), 1.35 (s, 9 H, *t*-Bu).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.7, 153.1, 152.3, 150.1, 149.1, 141.9, 140.9, 135.9, 129.4, 129.1, 127.5, 126.6, 124.6, 127.3, 123.3, 121.2, 83.4, 80.2, 28.5, 27.9, 26.8.

HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{25}H_{29}N_3O_5$: 452.2182; found: 452.2180.

Troc Deprotection; General Procedures

Method A

Activated Zn (392 mg, 6 mmol) was added to a solution of the Troc-protected compound (0.05 mmol) in glacial AcOH (5 mL). The suspension was stirred at r.t. until all the starting material had reacted (monitored by HPLC), then the mixture was filtered and the solid was washed with AcOH (2 × 2 mL). The filtrate was diluted with aq NH_4OH (10 mL, pH 10) and extracted with EtOAc (2 × 15 mL). The organic layers were collected, washed with H_2O (2 × 10 mL), brine (5 mL) and then evaporated to dryness.

Method B

Cd (581 mg, 5.17 mmol) was added to a solution of Troc-protected compound (0.05 mmol) in a mixture of DMF and glacial AcOH (1:1, 6 mL). The suspension was stirred at r.t. until all the starting material had reacted (monitored by HPLC), then the mixture was filtered and the solid was washed with DMF (2 × 2 mL). The solvent was evaporated to dryness under reduced pressure and the residue was dissolved in aq NH_4OH (10 mL, pH 10) and extracted with EtOAc (3 × 10 mL). The organic layers were collected, washed with H_2O (2 × 10 mL), brine (5 mL) and then evaporated to dryness.

Method C

Cd/Pb amalgam (10%, 394 mg, 3.5 mmol) was added to a solution of the Troc-protected compound (0.23 mmol) in a mixture of ammonium acetate (1 M, pH 7) and THF (1:1, 20 mL). The mixture was stirred at r.t. until all the starting material had reacted (monitored by HPLC), then filtered, and the solid was washed with THF (5 mL) and EtOAc (5 mL). The filtrate was extracted with EtOAc (2 × 10 mL) and the organic layer was washed with H_2O (5 mL), brine (5 mL) and then evaporated to dryness.

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