Practical Method for Chemoselective Formation of MTPA Amide Derivatives from Amino Alcohols and Phenols

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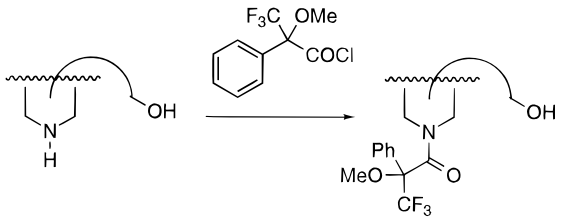
Recently, we reported that Mosher's MTPA (methoxy-(trifluoromethyl)phenylacetyl) technology could be used to deduce the absolute configuration (as well as the enantiomeric excess) of cyclic amines.[1] That work built upon earlier important studies by Rauk[2a,b] and Braekman.[2c] MTPA esters and amides of chiral alcohols and primary amines, respectively, are well known.[3] Other chiral derivatizing agents, including *O*-methylmandelic acid, have also been applied successfully to secondary alcohols and primary amines.[4]

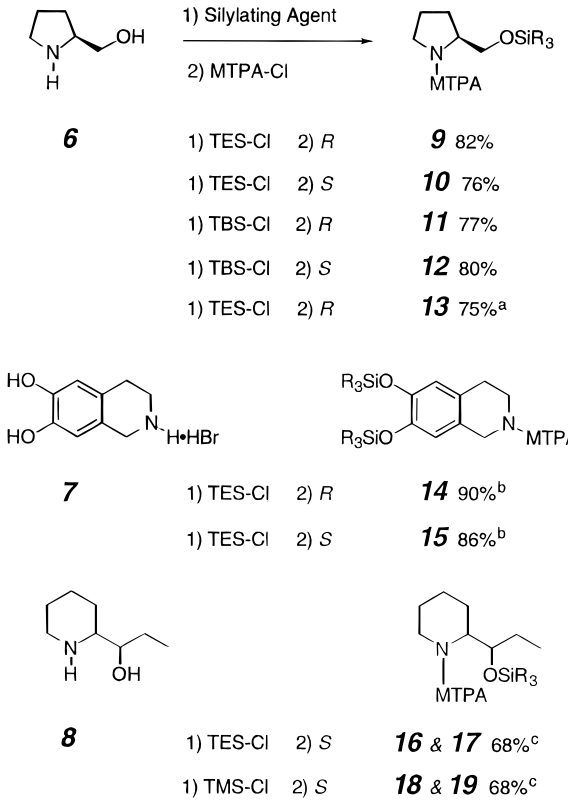
We were interested in applying MTPA amide technology to cyclic amines containing alcohol and/or phenol moieties (cf. **1** to **2**). While it is known that primary amino alcohols can be converted to MTPA amides without derivatization of the alcohol,[3e] conversion of cyclic amines into MTPA amides is a slow process, and our initial efforts to selectively install MTPA groups into amino alcohols were unsuccessful.



1 **2**

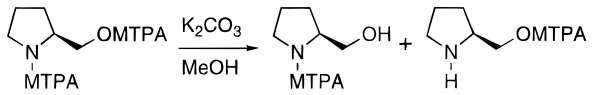
In addition, our attempts to install multiple MTPA groups into amino alcohols (to generate per-Mosher derivatives) generally resulted in poor yields. Even when successfully introduced, multiple MTPA moieties in one molecule have anisotropic effects that are not entirely predictable. Also, we found that removal of MTPA esters in the presence of MTPA amides proved to be surprisingly troublesome. For example, the bis-Mosher derivative arising from 2-pyrrolidinemethanol (**3**) produced only a moderate yield of both the mono-MTPA amide **4** and the mono-MTPA ester **5**.

Table 1. Amino Alcohol and Amino Phenol Substrates 6−8 and Their Conversion to MTPA-Amide Silyl Ethers 9−19



6	1) TES-Cl 2) *R*	***9*** 82%
	1) TES-Cl 2) *S*	***10*** 76%
	1) TBS-Cl 2) *R*	***11*** 77%
	1) TBS-Cl 2) *S*	***12*** 80%
	1) TES-Cl 2) *R*	***13*** 75%[a]
7	1) TES-Cl 2) *R*	***14*** 90%[b]
	1) TES-Cl 2) *S*	***15*** 86%[b]
8	1) TES-Cl 2) *S*	***16*** & ***17*** 68%[c]
	1) TMS-Cl 2) *S*	***18*** & ***19*** 68%[c]

[a] Quenched with TBAF to obtain the corresponding alcohol. [b] The analogous bis-TMS ethers were prepared but are too labile to be conveniently handled. [c] Combined yield of diastereomers after HPLC separation.



3 ***4*** ***5***

These issues prompted us to seek a one-pot method to install an MTPA amide group into a cyclic amine while leaving the alcohol or phenol portions of the molecule unperturbed. It was reported that *N*-acyl derivatives of aspartic acid could be prepared conveniently by first protecting the acid moieties as TMS esters.[5] We studied a similar strategy for the derivatization of substrates **6**−**8** as summarized in Table 1. Treatment of the substrate with various silylating agents followed by addition of MTPA-Cl resulted in derivatized amides in good yields. While TMS ethers were sufficient to prevent MTPA derivatization of the alcohols, they tended to cleave during chromatography, sometimes resulting in poor yields of the (trimethylsilyl)oxy MTPA-amides. TES and TBS ethers, on the other hand, are stable to chromatographic purification. Each can be removed subsequently using mild conditions (TBAF or HF/MeCN) that do not affect the amide group.

Alternatively, we found that directly quenching the reaction mixture used to produce the MTPA amide with either TBAF or HF/MeCN was effective for removal of any *O*-silyl groups before purification. Thus, amide

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alcohols or phenols were isolated directly following chromatography.

We chose (*S*)-2-pyrrolidinemethanol (prolinol, **6**); 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**7**); and 2-piperidine-2-propanol (conhydrine, **8**) as model compounds to probe the limits of the technique. The results of these experiments are shown in Table 1.

Clearly, this is a valuable technique for the derivatization of amines containing alcohol or phenol functionality. The yields for these several-step transformations are comparable to those for the single derivatizations of simple cyclic amines as described previously.[1]

Tetrahydroisoquinoline **7** was a useful model compound for uncovering reaction conditions potentially applicable to the michellamines,[6] a family of highly-oxygenated dimeric naphthyltetrahydroisoquinoline alkaloids that have shown promising anti-HIV activity. The described techniques were successfully applied to a series of structurally related compounds, including ancistrobrevine B.[7] The results of these experiments and analysis of the resulting spectral data will be described elsewhere.

Finally, it should be emphasized that this methodology is both practical and general. For example, other acylating agents (e.g., ethyl chloroformate) can be successfully used in place of the MTPA-Cl. Thus, the strategy should be applicable to a variety of chemoselective transformations of amines containing other hydroxyl functionality.

Experimental Section

All ^{1}H NMR chemical shifts are referenced to TMS (δ_{TMS} = 0.00) and all ^{13}C NMR shifts to $CDCl_3$ (δ_{CDCl3} = 77.0).

General Procedure: (*S*)-2-Pyrrolidinemethanol, Triethylsilyl Ether (*R*)-MTPA Amide (10). (*S*)-2-Pyrrolidinemethanol (61 mg, 0.60 mmol) and triethylamine (420 μL, 3.0 mmol, 5 equiv) were dissolved in methylene chloride and stirred at room temperature. Chlorotriethylsilane (125 μL, 0.744 mmol, 1.2 equiv) was added slowly, and the reaction mixture was stirred for 40 min. (*S*)-MTPA-Cl (125 μL, 0.668 mmol, 1.1 equiv) was then added dropwise, and the mixture was stirred for 14 h. The reaction mixture was concentrated under reduced pressure and taken up in 1 M NH_4Cl (5 mL). The insoluble brown oil was extracted into methylene chloride (3 × 12 mL), dried over $MgSO_4$, and concentrated under reduced pressure to leave a brown liquid (276 mg), which was purified by flash chromatography (SiO_2, 10:1 Hx:EtOAc) to give the (*R*)-MTPA amide **10** as a pale yellow liquid (199 mg, 82%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52−7.53 (m, 1H), 7.40−7.44 (m, 2H), 7.35−7.38 (m, 2H), 4.27 (dddd, 1H, J = 4, 4, 6, 8 Hz), 3.84 (dd, 1H, J = 3.5, 10 Hz), 3.81 (dd, 1H, J = 5.5, 10 Hz), 3.65 (q, 3H, J = 1.5 Hz), 3.41 (ddd, 1H, J = 7, 7, 11 Hz), 2.45 (ddd, 1H, J = 6, 7.5, 11 Hz), 1.92 (dddd, 1H, J = 4, 6, 7.5, 13 Hz), 1.82 (dddd, 1H, J = 5.5, 5.5, 5.5, 12.5 Hz), 1.74 (ddddd, 1H, J = 7, 7, 7.5, 7.5, 12.5 Hz), 1.63 (ddddd, 1H, J = 5.5, 5.5, 5.5, 7, 13.5 Hz), 0.94 (t, 9H, J = 7.5 Hz), 0.60 (q, 6H, J = 7.5 Hz); IR (thin film) 2955 (m), 1656 (s), 1265 (m), 1182 (s), 1163 (s) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 402 (80, $M^+ - CH_2CH_3$), 299 (14), 286 (47), 242 (21), 189 (100), 105 (11).

(*S*)-2-Pyrrolidinemethanol, Triethylsilyl Ether (*S*)-MTPA Amide (9). Prepared by the general procedure: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52−7.55 (m, 2H), 7.37−7.41 (m, 3H), 4.29 (dddd, 1H, J = 2.5, 4.5, 6, 8 Hz), 4.04 (dd, 1H, J = 4.5, 10.5 Hz), 3.70 (q, 3H, J = 1.5 Hz, OMe), 3.69 (dd, 1H, J = 2.5, 10.5 Hz), 3.18 (ddd, 1H, J = 6.5, 8.5, 11.5 Hz), 2.85 (ddd, 1H, J = 5, 7.5, 11.5 Hz), 1.89 (dddd, 1H, J = 6, 7.5, 8.5, 13 Hz), 1.70−1.82 (m, 2H), 1.30 (ddddd, 1H, J = 7.5, 7.5, 7.5, 9.5, 12.5 Hz), 0.94 (t, 9H, J = 8 Hz), 0.58 (q, 6H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8, 128.8, 127.8, 126.4, 61.5, 59.3, 54.5, 47.2, 25.7, 24.4, 6.31, 4.0; IR (thin film) 2955 (m), 1657 (s), 1263 (m), 1183 (s), 1163 (s) cm^{-1}; MS (EI) m/z (rel int) 402 (100, $M^+ - CH_2CH_3$), 299 (12), 286 (41), 242 (21), 189 (81), 105 (17).

(*S*)-2-Pyrrolidinemethanol, *tert*-Butyldimethylsilyl Ether (*S*)-MTPA Amide (11). Prepared by the general procedure: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51−7.53 (m, 2H), 7.36−7.39 (m, 3H), 4.30 (dddd, 1H, $J \approx$ 2.5, 4.5, 6.5, 8 Hz), 4.06 (dd, 1H, J = 4.5, 10 Hz), 3.70 (q, 3H, J = 1.5 Hz), 3.69 (dd, 1H, J = 2.5, 10 Hz), 3.18 (ddd, 1H, J = 6.5, 8, 11 Hz), 2.87 (ddd, 1H, J = 4.5, 7, 11.5 Hz), 1.87 (m, 1H, ΣJ's = 35 Hz), 1.71−1.82 (m, 2H), 1.31 (m, 1H, ΣJ's = 44 Hz), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 133.6, 129.2, 128.2, 126.8, 124.3 (q, J = 275 Hz), 62.3, 59.7, 54.9 (q, J < 2 Hz), 47.6, 25.9, 25.8, 24.8, 18.1, −5.5, −5.6; MS (EI, 70 eV): m/z (rel int) 416 (3, $M^+ - CH_3$), 374 (100), 290 (4), 286 (7), 189 (57), 105 (14).

(*S*)-2-Pyrrolidinemethanol, *tert*-Butyldimethylsilyl Ether (*R*)-MTPA Amide (12). Prepared by the general procedure: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51−7.53 (m, 2H), 7.34−7.38 (m, 3H), 4.28 (dddd, 1H, J = 3.5, 4, 5.5, 8.5 Hz), 3.86 (dd, 1H, J = 5.5, 10 Hz), 3.81 (dd, 1H, J = 3, 10 Hz), 3.65 (q, 3H, J = 1.5 Hz), 3.43 (ddd, 1H, J = 7, 7, 11 Hz), 2.45 (ddd, 1H, J = 6, 7.5, 11.5 Hz), 1.91 (dddd, 1H, J = 4, 5.5, 7, 12.5 Hz), 1.80 (dddd, 1H, J = 8, 8, 8, 12.5 Hz), 1.75 (ddddd, 1H, J = 7, 7, 7, 7, 12.5 Hz), 1.63 (ddddd, 1H, J = 6, 6, 7.5, 7.5, 12.5 Hz), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 133.8, 129.0, 128.1, 127.0, 123.8 (q, J = 290 Hz), 61.9, 59.8, 55.3 (q, J = 2.4 Hz), 47.0, 26.0, 25.9, 24.7, 18.2, −5.4$^+$; −5.4$^-$; IR (thin film) 2953 (m), 1654 (s), 1181 (s), 1163 (m), 1103 (m) cm^{-1}; MS (EI, 70 eV): m/z (rel int) 416 (3, $M^+ - CH_3$), 374 (100), 290 (4), 286 (10), 189 (45), 105 (11); HRMS (CI, isobutane) calcd for $C_{21}H_{33}F_3NO_3Si$ ($M + H^+$) 432.2182, found 432.2188.

(*S*)-2-Pyrrolidinemethanol (*S*)-MTPA Amide (13). (*S*)-2-Pyrrolidinemethanol (23 mg, 0.227 mmol) and triethylamine (150 μL, 1.1 mmol, 4.8 equiv) were dissolved in methylene chloride (1 mL) and stirred while chlorotriethylsilane (42 μL, 0.25 mmol, 1.1 equiv) was added via syringe. The reaction mixture was stirred for 10 min. DMAP (1 mg) and (*R*)-MTPA-Cl (47 μL, 0.25 mmol, 1.1 equiv) were added, and the mixture was stirred for 14 h. Added to the reaction mixture were methylene chloride (2 mL) and TBAF trihydrate (315 mg, 1 mmol, 4.5 equiv), and the mixture was stirred for 3 h. The mixture was diluted with water, the layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give an amber liquid (479 mg). This liquid was purified by flash chromatography (SiO_2, 1:1 Hx:EtOAc) to provide the *S*-amide **13** as a clear liquid (54 mg, 75%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47−7.48 (m, 2H), 7.39−7.41 (m, 3H), 4.39 (dddd, 1H, J = 3, 6, 7.5, 10.5 Hz), 4.26 (dd, 1H, J = 3.5 7.5 Hz), 3.72 (ddd, 1H, J = 3, 7.5, 11.5 Hz), 3.66 (q, 3H, J = 1.5 Hz), 3.66 (ddd, 1H, J = 3, 7.5, 11.5 Hz), 3.61 (ddd, 1H, J = 5.5, 7, 11.5 Hz), 2.37 (ddd, 1H, J = 7.5, 7.5, 12 Hz), 2.01 (dddd, 1H, J = 6.5, 6.5, 7.5, 13.5 Hz), 1.60−1.72 (m, 2H), 1.48 (dddd, 1H, J = 6, 7, 7, 13 Hz); IR (thin film) 3442 (br), 1652 (s), 1179 (s), 1163 (s), 1079 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 317 (4, M^+), 286 (26, $M^+ - CH_2OH$), 189 (100), 128 (80).

6,7-Bis(triethylsiloxy)-1,2,3,4-tetrahydroisoquinoline (*R*)-MTPA Amide (15). Amine hydrobromide **7** (20 mg, 0.081 mmol) was suspended in triethylamine (70 μL, 0.50 mmol, 6.2 equiv) and methylene chloride (1 mL) and stirred while chlorotriethylsilane (30 μL, 0.18 mmol, 2.2 equiv) was added slowly. The mixture was stirred for 45 min, and DMAP (2 mg) and (*S*)-MTPA-Cl (20 μL, 0.107 mmol, 1.3 equiv) were added. The mixture was then stirred overnight and concentrated under reduced pressure to leave an oily solid. This solid was taken up in 1 M NH_4Cl (1.5 mL), extracted into methylene chloride (3 × 2 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a brown liquid (58 mg). The liquid was purified by flash chromatography (SiO_2, 10:1 Hx:EtOAc) to provide the (*R*)-amide **15** as a clear oil (42 mg, 82%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53−7.54 (m, 2H), 7.45−7.47 (m, 2H), 7.37−7.40 (m, 3H, 7.22−7.26 (m, 3H), 6.56 (s, 1H), 6.49 (s, 1H), 6.40 (s, 1H),

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5.92 (s, 1H), 4.75 (d, 1H, J = 17 Hz), 4.58 (d, 1H, J = 17 Hz), 4.30 (d, 1H, J = 16 Hz), 4.09 (d, 1H, J = 16 Hz), 4.02 (ddd, 1H, J = 6, 6, 12.5 Hz), 3.72 (q, 3H, J = 1.5 Hz), 3.67 (ddd, 1H, J = 5, 8, 13 Hz), 3.64 (q, 3H, J = 1.5 Hz), 3.47 (ddd, 1H, J = 4, 8, 13 Hz), 3.38 (ddd, 1H, J = 5, 6.5, 13.5 Hz), 2.83 (ddd, 1H, J = 5.5, 8, 16 Hz), 2.70 (ddd, 1H, J = 5.5, 5.5, 16 Hz), 2.34 (ddd, 1H, J = 4.5, 6.5, 16 Hz), 1.96 (ddd, 1H, J = 5, 8, 16 Hz), 0.91−1.00 (m, 18H), 0.61−0.76 (m, 12H); IR (thin film) 2954 (m), 1654 (s), 1514 (s), 1269 (m), 1183 (m), 1161 (m) cm^{-1}; MS (EI, 70 eV) m/z (rel int) 578 (1, $M^+ - CH_2CH_3$), 392 (29), 391 (75), 362 (41), 189 (16), 115 (15), 87 (100), 59 (53). The ^1H NMR spectral data for **14**, the enantiomer of **15**, were identical to those for **15**.

α-Ethyl-2-piperidinemethanol Triethylsilyl Ether (*R*)-MTPA Amides (16 and 17). Prepared by the general procedure from conhydrine. HPLC separation gave rise to a major isomer having the following spectral data: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.56−7.57 (m, 2H), 7.38−7.40 (m, 3H), 4.63−4.67 (m, 1H), 4.10 (ddd, 1H, J = 4, 5.5, 9.5 Hz), 3.87 (dd, 1H, J = 4.5 ,14 Hz), 3.69 (q, 3H, J = 1.5 Hz), 2.89 (ddd, 1H, J = 3.5, 13.5, 13.5 Hz), 1.93 (dddd, 1H, J = 3.5, 3.5, 3.5, 13.5 Hz), 1.45−1.61 (m, 3H), 1.33−1.41 (m, 1H), 1.24−1.29 (m, 1H), 0.97 (t, 3H, J = 7 Hz), 0.95 (t, 9H, J = 7.5 Hz), 0.9 (m, 1H), 0.61 (dq, 3H, J = 7, 10 Hz), 0.60 (dq, 3H, J = 7, 9.5 Hz), 0.10 (ddddd, 1H, J = 5, 5, 12, 12, 12 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 129.1, 128.1, 126.8, 70.9, 55.5, 51.7, 41.2, 26.8, 23.2, 24.0, 18.8, 8.0, 7.0, 5.4; MS (EI, 70 eV) m/z (rel int) 454 (1, $M^+ - CH_2CH_3$), 444 (8), 415 (14), 300 (68), 189 (100), 173 (28), 115 (27); HRMS (CI, isobutane) calcd for $C_{24}H_{39}F_3NO_3Si$ ($M + H^+$) 474.2651, found 474.2649.

α-Ethyl-2-piperidinemethanol Trimethylsilyl Ether (*R*)-MTPA Amides (18 and 19). Prepared by the general procedure from conhydrine. HPLC separation gave rise to a major isomer having the following spectral data: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.56−7.57 (m, 2H), 7.38−7.41 (m, 3H), 4.63−4.66 (m, 1H), 4.04 (ddd, 1H, J = 5.5, 5.5, 8 Hz), 3.88 (dd, 1H, J = 5.5, 14 Hz), 3.70 (q, 3H, J = 1.5 Hz), 2.88 (ddd, 1H, J = 3.5, 13.5, 13.5 Hz), 1.92 (dddd, 1H, J = 3, 3, 3, 13.5 Hz), 1.42−1.60 (m, 3H), 1.32−1.39 (m, 1H), 1.27−1.29 (m, 1H), 0.96 (t, 3H, J = 7.5 Hz), 0.91 (br d, 1H, J = 13.5 Hz), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 129.1, 128.1, 126.8, 71.3, 55.6, 52.3, 41.1, 27.2, 23.4, 23.1, 18.7, 8.7, 0.7; MS (EI, 70 eV) m/z (rel int) 416 (3, $M^+ - CH_3$), 373 (9), 300 (45), 189 (100), 131 (18); HRMS (CI, isobutane) calcd for $C_{21}H_{33}F_3NO_3Si$ ($M + H^+$) 432.2182, found 432.2124; calcd for $C_{15}H_{17}F_3NO_2$ (M^+ − TMSOCHEt) 300.1211, found 300.1216.

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