Pergamon

Tetrahedron Letters 42 (2001) 8215–8217

TETRAHEDRON LETTERS

Facile and purification free synthesis of Mosher amides utilizing a ROMPgel supported reagent

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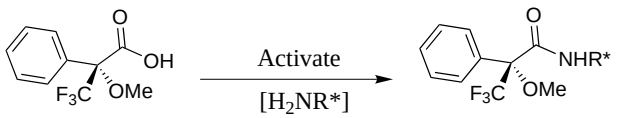
Received 25 July 2001; revised 5 September 2001; accepted 13 September 2001

Abstract—A novel ROMPgel immobilized active ester for the purification free synthesis of Mosher amides is described.

The evaluation of enantiomeric purity of both natural and synthetic compounds is of fundamental importance in organic chemistry. Over the past four decades, an arsenal of spectroscopic techniques have been developed for the determination of enantiomeric purity and absolute stereochemistry, including chromatography utilizing an asymmetric stationary phase,[1] NMR spectroscopy utilizing chiral solvating reagents,[2] the synthesis and assay of diastereoisomeric derivatives[3] and the application of chiral shift reagents.[4] However one of the most convenient methods for determining the enantiomeric excess of chiral amines is the formation of the corresponding diastereomeric amides, thus allowing calculation of the diastereoisomer ratio using ^{1}H NMR (Scheme 1).

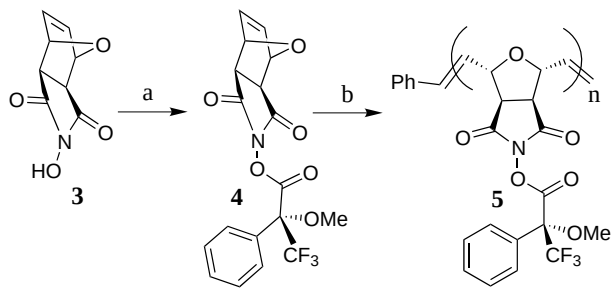


1 2

Scheme 1.

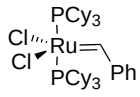
In 1972, α-methoxy-α-trifluoromethylphenylacetic acid (MTPA)[5] **1** was first applied to this task having the inherent advantage that ^{19}F NMR chemical shift differences for the α-CF_3 group (of each diastereoisomer) are generally greater than those of the corresponding proton signals in the same compounds. Typically, the synthesis of Mosher amides can be achieved using an array of coupling agents such as DCC,[6] EDC[7] and BOP.[8] However, the resultant amides often require purification prior to analysis, potentially leading to inaccuracies in measurements. The opportunity therefore existed for the development of a solid support MTPA transfer agent, which would eliminate the need for further purification and be amenable for the determination of enantiomeric excesses in a parallel array directly in an NMR tube.

The Barrett group has utilized ROMPgel supported *N*-hydroxysuccinimide esters which afford the corresponding amides in excellent yields when allowed to react with primary and secondary amines.[9] Thus, we wish to report the development of a ROMPgel supported activated Mosher ester as a means to performing a high yielding purification free synthesis of Mosher amides.



3 4 5

Scheme 2. *Reagents and conditions*: (a) **1**, DIC, CH_2Cl_2, 25°C, 12 h, 95%; (b) **6** (0.5 mol%), **7** (20 mol%), CH_2Cl_2, 25°C, 12 h.



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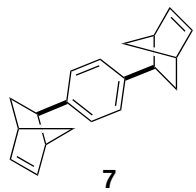

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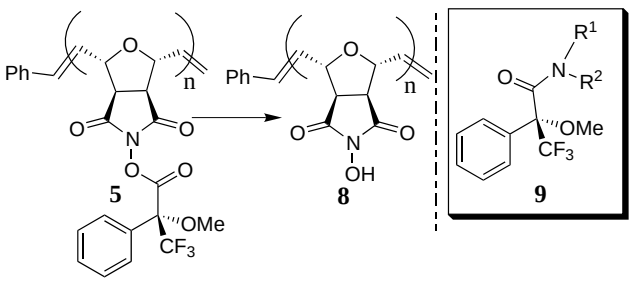
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01724-5

Our strategy was to synthesize the monomer **4** which could be polymerized to afford an insoluble ROMPgel upon treatment with Grubbs' catalyst (Scheme 2). This was achieved by performing a DIC coupling of the commercially available acid **1** with the hydroxyimide **3** to give the *N*-hydroxysuccinimide ester **4** in 95% yield. The polymerization of alkene **4** was carried out using the Grubbs' catalyst **6** and 20% of crosslink **7** to afford the desired insoluble polymer **5**. We observed that increasing the amount of Grubbs' catalyst had a detrimental effect on the quality of the polymer with regards to the coloration and solubility of the polymer. The loading was also effected, as a larger quantity of crosslinker had to be added to obtain a polymer of satisfactory insolubility. The polymerization was terminated with ethyl vinyl ether and the resultant polymer **5** was subsequently washed with CH_2Cl_2 and dried to afford a white polymer having a loading of 2.1 mmol/g in 75% yield.

Previously, the Barrett group has reported the reactivity of ROMPgel *N*-hydroxysuccinimide esters towards transacylation using amines as nucleophiles.[9] Thus, we chose a series of primary and secondary amines to demonstrate their effectiveness in Mosher amide synthesis (Table 1). The ROMPgel Mosher ester **5** was allowed to react with 0.8 equivalents of the appropriate amine in CH_2Cl_2, $CDCl_3$ or $CDCl_3$ and heated to 40°C. After the appropriate reaction time, depending on the nucleophilicity of the amine, the polymer was simply filtered off through a pad of Celite and filtrate concentrated to afford the desired amides in excellent yield and high purity (Scheme 3).

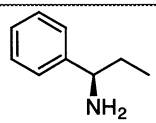
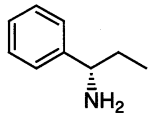
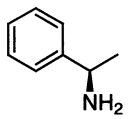
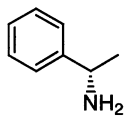
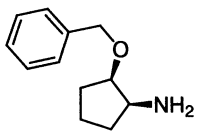
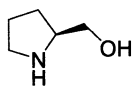
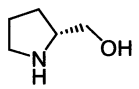
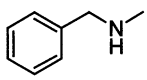
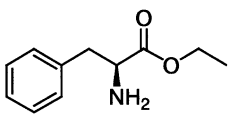
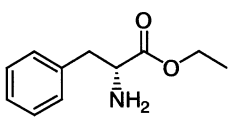
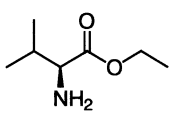
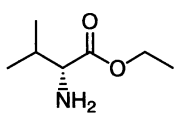


Scheme 3.

As well as being effective for primary amines (entries **9a–e**), the ROMPgel Mosher reagent **5** was also found to be applicable to secondary amines (**9f–h**). Chemoselectivity was demonstrated in entries **9f** and **9g** in which the Mosher amides were selectively formed in the presence of alcohol functionality.

Finally, the preparation of α-amino ester derivatives[10] was shown to be possible by our method, as exemplified in entries **9i–l**. Thus, a simple and efficient method for the determination of enantiomeric excess, using a solid support Mosher transacylation reagent, has been developed. The preparation of amide **9** could be easily carried out within an NMR tube with direct recording of the spectra after completion of the reaction.[11]

Table 1.

Entry	Amine	Reaction Time	Yield
9a		6 h	90%
9b		6 h	88%
9c		6 h	90%
9d		6 h	91%
9e		12 h	94%
9f		24 h	82%
9g		24 h	80%
9h		24 h	84%
9i		24 h	87%
9j		24 h	85%
9k		24 h	86%
9l		24 h	91%

Isolated yields, > 95% purity as determined by GCMS and ^{1}H NMR.

Conclusion

To conclude, we have demonstrated the synthetic utility of the ROMPgel supported *N*-hydroxysuccinimide ester **5** for the formation of Mosher amides, with minimal purification. Excellent yields and purity were obtained for a range of primary and secondary amines as well as amino esters, thus highlighting the considerable practical advantage over more conventional solution phase methods for the determination of ee in parallel arrays.

Acknowledgements

We thank Merck KGaA for generous support of this research. Additionally we thank GlaxoSmithKline for the valuable endowment (to A.G.M.B.), the EPSRC and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.

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9. (a) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zécri, F. *Org. Lett*. **2000**, *2*, 261–264; (b) Barrett, A. G. M.; Cramp, S. M.; Roberts, R. S.; Zécri, F. J. *Comb. Chem. High Throughput Screen*. **2000**, *3*, 131–138.
10. The preparation of the D-amino esters were achieved using the literature procedure described by Bergel, F.; Johnson, J. M.; Wade, R. *J. Chem. Soc*. **1962**, 3802–3814.
11. **Typical procedure**: (*R*)-(+)-α-Methylbenzylamine (14.2 mg, 0.12 mmol) was added to a suspension of the ROMPgel Mosher ester **5** (75 mg, 0.1 mmol) in $CHCl_3$ (5 mL) and was heated to 40°C. The resulting mixture was filtered through a short plug of Celite and washed with $CHCl_3$ (2 mL). The solvent was removed under a stream of nitrogen to afford the amide (36 mg, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, $J=7.0$ Hz, 3H), 3.39 (s, 3H), 5.22 (q, $J=7.6$ Hz, 1H), 7.03 (br d, $J=7.5$ Hz, 1H), 7.36 (m, 6H), 7.44 (m, 2H), 7.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 48.8, 55.0, 84.1 (q, $J=32$ Hz, C-CF_3), 123.8 (q, $J=288$ Hz, CF_3), 126.2, 127.6, 127.7, 128.6, 128.8, 129.5, 132.6, 142.3, 165.4; IR (KBr) 3324, 2929, 1684, 1511, 1379, 1266, 1165, 913 cm^{-1}; MS (EI, m/z); 77 (14), 105 (100), 189 (42), 262 (6), 294 (33), 305 (31), 322 (11), 337 (34), calcd for $C_{18}H_{18}F_3NO_2$: ($M^{+\bullet}$) 337.1289, found ($M^{+\bullet}$) 337.1288.