Direct Carbon–Carbon Bond Formation via Soft Enolization of Thioesters: An Operationally Simple Mannich Addition Reaction

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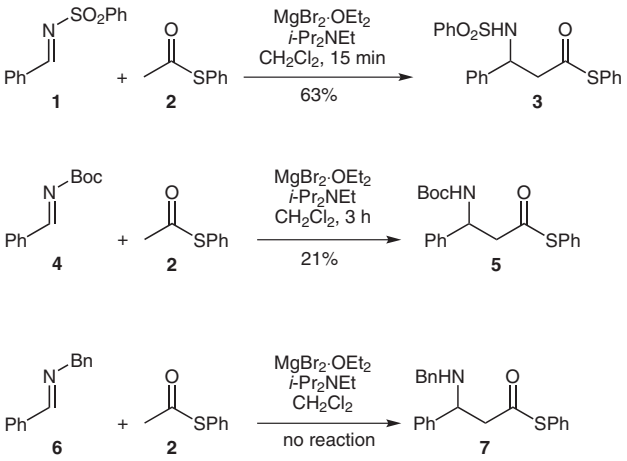
Abstract: Thioesters undergo soft enolization and direct Mannich addition to sulfonylimines on treatment with magnesium bromide ethyl etherate and *N*,*N*-diisopropylethylamine. The reactions proceed readily with a range of sulfonylimines and, in the case of 2,4,6-triisopropylphenyl thiopropionate, give moderate to good *syn* diastereoselectivity.

Key words: enolates, imines, Mannich addition reactions, magnesium, thioesters

The Mannich addition reaction provides a convenient approach to the synthesis of β-amino acid derivatives, which are extremely important compounds in organic and medicinal chemistry.[1] Typically, Mannich reactions are carried out using a preformed enolate species, along with one of a variety of different imine derivatives (sulfonylimine, alkyl imine,[2] etc.). While effective, the step-wise procedures required to generate the enolates are time-consuming, particularly if trapping is involved, and require that all manipulations be conducted under anhydrous conditions and, when strong bases are used, at low temperature. In contrast, soft enolization[3,4] provides a mild and straightforward approach to conducting enolate chemistry. Here, rather than forcing deprotonation with a strong base such as lithium diisopropylamide (LDA), a relatively weak basic amine is used in combination with a Lewis acid to effect deprotonation. We have been investigating this mode of enolization with thioesters in the context of direct aldol additions and direct crossed Claisen coupling reactions.[5] Given the efficiency and operational simplicity of these soft enolization-based transformations, we sought to extend this approach to the synthesis of β-amino acid derivatives. In this report, we describe the development of a magnesium bromide ethyl etherate ($MgBr_2{\cdot}OEt_2$) promoted direct Mannich addition reaction between thioesters and sulfonylimines using soft enolization.

We began our studies by establishing whether soft enolization could indeed be used to facilitate a direct Mannich reaction. This was done by combining commercially available *S*-phenyl thioacetate (**2**) and various imines (**1**, **4**[6] and **6**)[7] in dichloromethane, in the presence of magnesium bromide ethyl etherate and *N*,*N*-diisopropylethylamine (DIPEA; Scheme 1). Of the imines tested, only the sulfonylimine **1** reacted cleanly and with acceptable yield. Whereas imine **4** did produce the desired addition product **5**, it did so to only a very small extent and produced several unidentified byproducts. No Mannich addition (→**7**) occurred in the reaction between **6** and **2**. Instead, *N*-benzylamine, benzaldehyde and **2** were isolated following workup.



Scheme 1 Model studies of the $MgBr_2{\cdot}OEt_2$-promoted Mannich addition employing soft enolization.

Having established the viability of the desired transformation, we investigated its scope with various sulfonylimines (Table 1).[8] The sulfonylimines used ranged from electron-rich to electron-poor, and also included an α,β-unsaturated system (**11**). In general, the reactions proceeded readily and gave yields ranging from 57–74%. In addition, a small amount (up to ~10%) of the corresponding β-lactam was obtained in each case.

Next, we turned our attention to the issue of diastereoselectivity in the case of the propionate thioester Mannich addition. To this end, sulfonylimine **1** and *S*-phenyl thiopropionate[9] (**16**) were combined under the soft enolization conditions described above. Unfortunately, while the reaction proceeded rapidly and with very good conversion, it showed no appreciable diastereoselectivity (Table 2, entry 1). In an effort to improve the selectivity of the transformation, a variety of propionate thioesters were examined, each of which differed in the steric bulk of the thiol component used to prepare them. While the *S*-ethyl thioester **17** also failed to react diastereoselectively, the more bulky *S*-*tert*-butyl species **18** gave a 2.2:1

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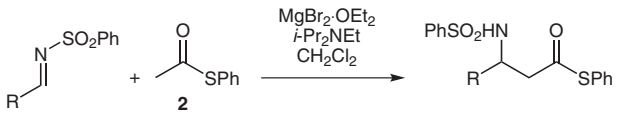
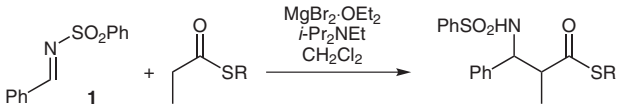
Table 1 Scope of the $MgBr_2{\cdot}OEt_2$-Promoted Thioester Mannich Addition Reaction Using Thioester **2**



Entry	Sulfonylimine (R)	Time (min)	Product	Yield (%)
1	**1** (Ph)	15	**3**	63
2	**8** (4-ClC_6H_4)	30	**12**	67
3	**9** (4-$MeOC_6H_4$)	60	**13**	74
4	**10** (2-MeC_6H_4)	120	**14**	73
5	**11** [(*E*)-CHCHPh]	30	**15**	57

Table 2 Effect of Thioester on Diastereoselectivity

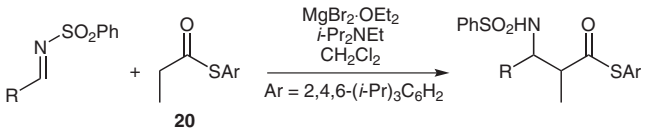


Entry	Thioester (R)	Time (h)	Product	*syn*/*anti*	Conversion (%)
1	**16** (Ph)	2	**21**	1.1:1	92
2	**17** (Et)	3	**22**	1.1:1	70
3	**18** (*t*-Bu)	3	**23**	2.2:1	74
4	**19** [2,6-$(Me)_2C_6H_3$]	6	**24**	3.1:1	78
5	**20** [2,4,6-$(i\text{-}Pr)_3C_6H_2$]	6	**25**	5.2:1	62

syn/*anti* ratio. A greater proportion of the *syn* diastereomer was produced when the even bulkier thioesters **19** and **20** were used, with the latter giving a *syn*/*anti* ratio of 5.2:1 (see experimental section for *syn* and *anti* assignments).

Using thioester **20**, the scope of the reaction was tested with each of the sulfonylimines used previously (Table 3). Once again, good to very good conversions were obtained, with *syn*/*anti* ratios ranging from 2.1:1 to 5.3:1.

Table 3 Scope of the $MgBr_2{\cdot}OEt_2$-Promoted Thioester Mannich Addition Reaction Using Thioester **20**



Entry	Sulfonylimine (R)	Time (h)	Product	*syn*/*anti*	Conversion (%)
1	**1** (Ph)	12	**25**	5.3:1	73
2	**8** (4-ClC_6H_4)	12	**26**	2.6:1	80
3	**9** (4-$MeOC_6H_4$)	12	**27**	4.6:1	66
4	**10** (2-MeC_6H_4)	12	**28**	2.4:1	80
5	**11** [(*E*)-CHCHPh]	12	**29**	2.1:1	61

In conclusion, we have developed a simple, direct Mannich addition reaction based on $MgBr_2{\cdot}OEt_2$-promoted soft enolization of thioesters. The reaction proceeds readily with a range of sulfonylimines and, in the case of 2,4,6-triisopropylphenyl thiopropionate, gives moderate to good diastereoselectivity in favor of the *syn* isomer.

Unless stated to the contrary, where applicable, the following conditions apply: Reactions were carried out using dried solvents (see below) under a slight static pressure of Ar (pre-purified quality), which had been passed through a column (5 × 20 cm) of Drierite. Glassware was dried in an oven at 120 °C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Reactions were stirred magnetically using Teflon-coated magnetic stirring bars. Teflon-coated magnetic stirring bars and syringe needles were dried in an oven at 120 °C for at least 12 h prior to use then cooled in a desiccator cabinet over Drierite. Hamilton microsyringes were dried in an oven at 60 °C for at least 24 h prior to use and cooled in the same manner. Commercially available Norm-Ject disposable syringes were used. Anhydrous benzene, toluene, Et_2O, CH_2Cl_2, THF, MeCN and DME were obtained using an Innovative Technologies solvent purification system. All other anhydrous solvents were of anhydrous quality purchased from Sigma–Aldrich. Commercial grade solvents were used for routine purposes without further purification. Et_3N, pyridine, DIPEA, 2,6-lutidine, *i*-Pr_2NH, and TMEDA were distilled from CaH_2 under a N_2 atmosphere prior to use. Flash column chromatography was performed on silica gel 60 (32–63 μm). ^1H and ^{13}C NMR spectra were recorded on a Varian spectrometer (400 MHz and 100 MHz, respectively) at ambient temperature. All ^1H chemical shifts are reported in ppm (δ) relative to TMS (δ = 0.00 ppm); ^{13}C shifts are reported in ppm (δ) relative to $CDCl_3$ (δ = 77.16 ppm). Diastereomeric ratios and percent conversions were determined by ^1H NMR analysis of the crude materials.

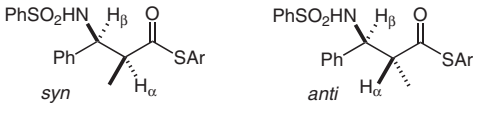
Assignment of *syn* and *anti* Configuration

A crystal structure was obtained for the major diastereomer of **25**, which was determined to have the *syn*-configuration. Assignment of the *syn* and *anti* diastereomers of **26**–**28** was done by comparison of their ^1H NMR spectra to that of **25**. In each case, the major (*syn*) isomer showed an apparent H_β triplet, whereas the minor (*anti*) isomer showed a H_β doublet of doublets (Table 4).

Synthesis of 25; Typical Procedure

$MgBr_2{\cdot}OEt_2$ (0.181 g, 0.70 mmol) was added to a stirred solution of thioester **20** (0.175 g, 0.60 mmol) and *N*-benzylidenebenzenesulfonamide (**1**; 0.123 g, 0.50 mmol) in CH_2Cl_2 (2.5 mL), followed

Table 4 Selected ^1H NMR Shifts and Coupling Constants for Compounds **25**–**28**



Ar = 2,4,6-(*i*-Pr)$_3C_6H_2$

Compd	*syn* H_β (δ)	*anti* H_β (δ)
25	4.46 (app t, *J* = 9.2 Hz)	4.67 (dd, *J* = 4.4, 9.6 Hz)
26	4.44 (app t, *J* = 9.2 Hz)	4.65 (dd, *J* = 4.4, 8.8 Hz)
27	4.40 (app t, *J* = 9.4 Hz)	4.62 (dd, *J* = 4.8, 9.2 Hz)
28	4.77 (app t, *J* = 9.8 Hz)	4.86 (dd, *J* = 4.4, 9.2 Hz)

by DIPEA (0.17 mL, 1.0 mmol). Stirring was continued for 12 h, then EtOAc (2.5 mL) and aq. HCl (10% v/v, 2.5 mL) were added. Stirring was continued for 5 min then the mixture was diluted in EtOAc (50 mL). The aqueous phase was extracted with EtOAc (3×10 mL) and the combined organic extracts were washed with brine (1×5 mL), dried ($MgSO_4$), and evaporated to give a light-yellow oil. Flash chromatography over silica gel (EtOAc–hexanes, 10:90→15:85) gave **25** *syn* and *anti* as pure, colorless solids.

25 (*syn*)
Yield: 0.130 g (48.3%); colorless solid.

^{1}H NMR ($CDCl_3$): δ = 7.61–7.56 (m, 2 H), 7.41–6.90 (m, 10 H), 5.67 (d, *J* = 9.2 Hz, 1 H), 4.46 (t, *J* = 9.2 Hz, 1 H), 3.32–3.14 [m, 2 H, including a qd at δ = 3.27 (*J* = 6.8, 9.2 Hz)], 2.83 (sept, *J* = 6.8 Hz, 1 H), 2.43–2.27 (m, 1 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.20 (d, *J* = 6.8 Hz, 6 H), 1.13–1.03 (m, 6 H), 0.88–0.75 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ = 199.6, 152.6, 152.1, 151.2, 140.5, 138.4, 132.4, 128.8, 128.5, 127.8, 127.4, 127.2, 122.0 (2 overlapping peaks), 120.9, 60.6, 54.0, 34.4, 31.8, 31.5, 24.5, 24.2, 23.94, 23.91, 23.6, 23.2, 16.4.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{39}NNaO_3S_2$: 560.2; found: 560.3.

25 (*anti*)
Yield: 0.025 g (9.3%); colorless solid.

^{1}H NMR ($CDCl_3$): δ = 7.61–7.56 (m, 2 H), 7.40–6.97 (m, 10 H), 6.23 (d, *J* = 9.2 Hz, 1 H), 4.67 (dd, *J* = 4.4, 9.6 Hz, 1 H), 3.36–3.22 [m, 2 H, including a dq at δ = 3.30 (*J* = 4.4, 6.8 Hz)], 2.87 (sept, *J* = 6.8 Hz, 1 H), 2.69–2.57 (m, 1 H), 1.40 (d, *J* = 7.2 Hz, 3 H), 1.23 (d, *J* = 6.8 Hz, 6 H), 1.18–1.09 (m, 6 H), 1.02–0.85 (m, 6 H).

^{13}C NMR ($CDCl_3$): δ = 202.6, 152.7, 152.1, 151.6, 141.2, 138.9, 132.2, 128.7, 128.4, 127.4, 126.8, 126.4, 122.2 (2 overlapping peaks), 120.7, 60.6, 53.1, 34.5, 32.0, 31.6, 24.6, 24.2, 24.0, 23.9, 23.7, 23.4, 17.2.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_{31}H_{39}NNaO_3S_2$: 560.2; found: 560.3.

29 (*syn*)
^{1}H NMR ($CDCl_3$): δ = 7.84–7.78 (m, 2 H), 7.45–7.00 (m, 10 H), 6.17 (d, *J* = 16.0 Hz, 1 H), 5.82 (dd, *J* = 8.4, 16.0 Hz, 1 H), 5.35 (d, *J* = 8.8 Hz, 1 H), 4.08 (app q, *J* = 7.6 Hz, 1 H), 3.34–3.05 [m, 3 H, including an app pent at δ = 3.10 (*J* = 6.8 Hz)], 2.88 (sept, *J* = 7.2 Hz, 1 H), 1.40 (d, *J* = 7.2 Hz, 3 H), 1.24 (d, *J* = 7.2 Hz, 6 H), 1.16–0.96 (m, 12 H).

^{13}C NMR ($CDCl_3$): δ = 201.1, 152.6, 152.2, 151.5, 141.0, 135.9, 134.2, 132.6, 129.0, 128.5, 128.2, 127.4, 126.6, 124.7, 122.2 (2 overlapping peaks), 120.8, 59.4, 52.6, 34.4, 32.0, 24.4, 24.2, 23.9, 23.6, 23.5, 15.6.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{41}NNaO_3S_2$: 586.2; found: 586.4.

29 (*anti*)
^{1}H NMR ($CDCl_3$): δ = 7.83–7.77 (m, 2 H), 7.46–6.98 (m, 10 H), 6.26 (d, *J* = 16.0 Hz, 1 H), 5.85 (dd, *J* = 6.6, 16.0 Hz, 1 H), 5.75 (d, *J* = 9.2 Hz, 1 H), 4.28–4.19 (m, 1 H), 3.40–3.02 [m, 3 H, including a dq at δ = 3.19 (*J* = 4.0, 7.0 Hz)], 2.88 (sept, *J* = 6.8 Hz, 1 H), 1.39 (d, *J* = 7.0 Hz, 3 H), 1.30–0.84 [m, 18 H, including a d at δ = 1.24 (*J* = 6.8 Hz)].

^{13}C NMR ($CDCl_3$): δ = 202.7, 152.6, 152.2, 151.6, 141.7, 135.9, 132.4 (2 overlapping peaks), 129.0, 128.5, 128.1, 127.1, 126.7, 126.5, 122.2 (2 overlapping peaks), 120.7, 58.8, 51.5, 34.5, 32.0, 24.3, 24.2, 24.0, 23.9, 23.7, 23.4, 16.2.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_{33}H_{41}NNaO_3S_2$: 586.2; found: 586.4.

3
^{1}H NMR ($CDCl_3$): δ = 7.73–7.64 (m, 2 H), 7.51–7.02 (m, 13 H), 5.75 (d, *J* = 7.6 Hz, 1 H), 4.82 (q, *J* = 6.8 Hz, 1 H), 3.16 and 3.06 (d AB q, J_{AB} = 40.7 Hz, *J* = 6.4, 15.6 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 195.7, 140.3, 138.8, 134.5, 132.6, 129.8, 129.4, 129.0, 128.7, 128.1, 127.2, 126.9, 126.6, 55.2, 49.6.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{19}NNaO_3S_2$: 420.1; found: 420.1.

15
^{1}H NMR ($CDCl_3$): δ = 7.86–7.81 (m, 2 H), 7.51–7.11 (m, 13 H), 6.33 (d, *J* = 16.0 Hz, 1 H), 5.92 (dd, *J* = 7.2, 16.0 Hz, 1 H), 5.42 (d, *J* = 8.4 Hz, 1 H), 4.44–4.34 (m, 1 H), 3.02 (d, *J* = 5.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 195.9, 140.8, 135.8, 134.5, 132.6, 129.8, 129.4, 129.1, 128.6, 128.1, 127.2, 126.8, 126.6, 126.5 (2 overlapping peaks), 53.5, 48.4.

ESI-MS: *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}NNaO_3S_2$: 446.1; found: 446.2.

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(9) Thioester **17** is commercially available (Aldrich). **16**, **18** and **19** were prepared from the corresponding commercially available (Aldrich) thiols under typical conditions.[5a] The thiol used in the synthesis of **20** was prepared according to: Garrattz, D. G.; Beaulieu, P. L. *Can. J. Chem.* **1980**, *58*, 2737.