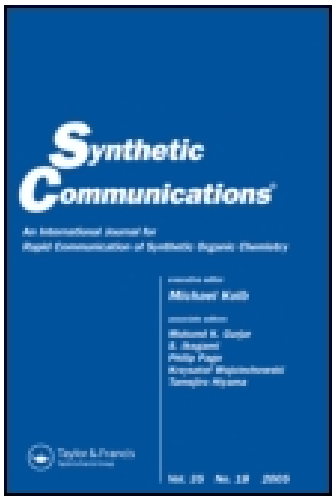

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A ONE-STEP PROTOCOL FOR THE N-CHLOROMETHYLATION OF HETEROCYCLIC IMIDES

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A ONE-STEP PROTOCOL FOR THE *N*-CHLOROMETHYLATION OF HETEROCYCLIC IMIDES

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ABSTRACT

A convenient single step methodology for the *N*-chloromethylation of heterocyclic imides using a mixture of formaldehyde sodium bisulfite adduct and thionyl chloride is described.

We have recently described the structure-based design of the 1,2,5-thiadiazolidin-3-one 1,1 dioxide template **I** and have demonstrated that it can serve as a general and flexible platform for the design of inhibitors of clinically-relevant (chymo)trypsin-like serine proteases.[1–5] We have furthermore demonstrated that core structure **I** is amenable to the facile construction of libraries for use in lead identification and optimization. As part of a project focusing on the solution phase construction of libraries

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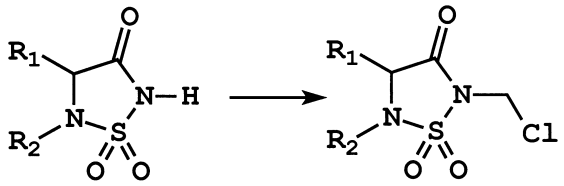

I Ia

based on **I**, a chloromethylation protocol suitable for generating intermediate **Ia** was desired.

Several procedures have been described in the literature for the direct or indirect *N*-chloromethylation of imide type molecules, including chlorotrimethylsilane/paraformaldehyde,[6] *N*-alkylation with HBr/HCHO/HOAc,[7] *N*-alkylation with chloromethyl pivalate[8] or chloromethyl phenyl sulfide[1–5] followed by treatment with HBr/HOAc or sulfuryl chloride, respectively, and others. After extensive experimentation, it was observed that refluxing a mixture of imide, sodium formaldehyde bisulfite adduct and thionyl chloride yielded the desired *N*-chloromethylated product. To the best of our knowledge, the use of these reagents and conditions for *N*-chloromethylation has not been described before.

The scope of this methodology was investigated using a range of substrates (Table 1). Thus, 4,5-disubstituted 1,2,5-thiadiazolidin-3-one 1,1 dioxide derivatives **1a** and **2a** yielded the corresponding *N*-chloromethylated products **1b** and **2b** upon refluxing a mixture of the heterocyclic imide with formaldehyde sodium bisulfite adduct and thionyl chloride. The reaction proceeded uneventfully when a compound bearing an ester group (**5a**) was used. The methodology was then extended to other heterocyclic systems with mixed results. Thus, isothiazolidin-3-one 1,1 dioxide derivative **3a** and saccharin **4a** yielded the desired products **3b** and **4b** in 64% and 73% yield, respectively. In the case of phthalimide and succinimide starting materials and minor amounts of unidentifiable products were recovered.

In summary, a convenient, one-step procedure for the *N*-chloromethylation of heterocyclic imides that is suitable for the solution phase construction of libraries has been described.

Representative Synthesis: A mixture of compound **1a** (2.47 g; 9.41 mmol), formaldehyde sodium bisulfite adduct (6.31 g; 47.05 mmol) and thionyl chloride (15 mL) was refluxed gently overnight. Excess thionyl chloride was removed *in vacuo* and the residue taken up in methylene chloride (80 mL). Saturated sodium bicarbonate (30 mL) was carefully added and

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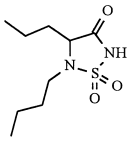
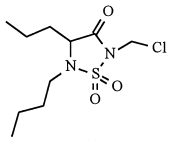
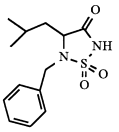
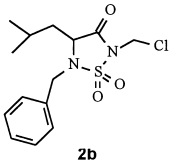
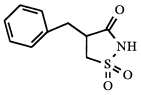
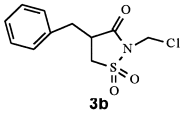
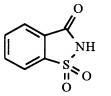
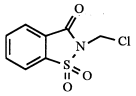
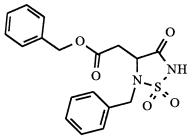
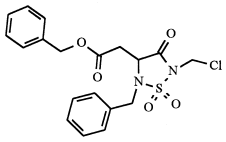
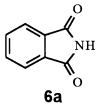
Table 1. Synthesis of *N*-Chloromethyl Compound

Starting Material	Product	% Yield	Melting Point (0C)
 1a	 1b	91	oil
 2a	 2b	97	oil
 3a	 3b	64	138 - 140
 4a	 4b	73	140 - 142
 5a	 5b	74	102 - 103
 6a	—b		
 7a	—b		

[b] starting material recovered

the organic layer was separated, washed with water (30 mL) and dried over anhydrous sodium sulfate. Removal of the solvent yielded **1b** (2.68 g; 91.0% yield). ^{1}H NMR($CDCl_3$): δ 0.98–2.0 (m, 18H), 3.08 (m, 1H), 3.40 (m, 1H), 4.00 (t, H), 5.36 (s, 2H). Anal. Calculated: %C: 46.31; %H: 7.45; %N: 9.00. Found: %C: 46.32; %H: 7.91; %N: 8.95.

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Compounds **2b**, **3b**, **4b** and **5b** were synthesized using a similar procedure.

Compound **2b**: δ 0.68 (d, 3H), 0.80 (d, 3H), 1.55–1.78 (m, 3H), 3.92 (t, 1H), 4.28 (d, 1H), 4.53 (d, 1H), 5.5 (d, 2H), 7.38 (s, 5H). Anal. Calcd. %C: 50.78; %H: 5.79; %N: 8.47. Found: %C: 50.78; %H: 5.83; %N: 8.42. Compound **3b**: δ 2.92 (1H, m), 3.36 (1H, m), 3.66 (1H, m), 3.80 (1H, m), 3.92 (1H, m), 5.50 (2H, q), 7.20–7.40 (5H, m). Anal. Calcd. %C: 48.22; %H: 4.42; %N: 5.12. Found: %C: 48.08; %H: 4.63; %N: 5.14. Compound **4b**: δ 5.58 (s, 2H), 7.26–7.93 (m, 3H), 8.14 (m, 1H), mp 140–2°C (lit.[9] mp 146–7°C). Compound **5b**: 2.70 (dd, 1H), 2.96 (dd, 1H), 4.31 (t, 1H), 4.50 (dd, 2H), 5.09 (dd, 2H), 5.26 (dd, 2H), 7.40 (m, 10H). Anal. Calcd. %C: 53.97; %H: 4.53; %N: 6.62. Found: %C: 54.06; %H: 4.73; %N: 6.76.

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