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Salts of Mosher's thioacid: agents for determining the enantiomer excess of S_N2 substrates

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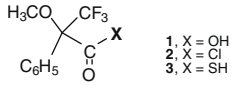
ABSTRACT

The racemic and the (*S*)-enantiomer of Mosher's thioacid, 2-methoxy-2-trifluoromethylphenylacetic thioacid, form air-stable salts with Proton Sponge [1,8-bis(dimethylamino)naphthalene]. These salts are powerful nucleophiles that react cleanly (S_N2 inversion) in $CDCl_3$ with optically active alkyl halides ranging in reactivities from unactivated alkyl bromides and iodides to benzylic bromides. The diastereomeric excess (de) of the thioester products indicates the enantiomeric excess (ee) of the starting alkyl halides.

Occasionally in the accounts of science, modifications and extensions of the art that would obviously be useful are overlooked. As time passes, the very obviousness of such modifications can deter further study—presumably the result of our tendency to think that seemingly obvious things must have been tried and must have encountered problems. This reasoning can be faulty. This report examines such a case: the utility of Mosher's thioacid.

Mosher's acid,[1] 2-methoxy-2-trifluoromethylphenylacetic acid (**1**), and the corresponding acid chloride (**2**), have found extensive use as agents for determining the enantiomeric excess[2a] (ee) of amines and alcohols and for predicting their absolute configurations.[2b,c]



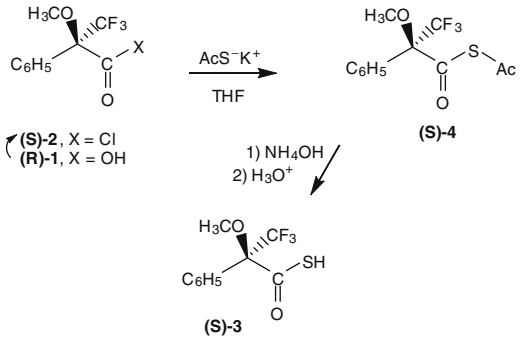
1, X = OH
2, X = Cl
3, X = SH

Considering this, and the well-known potent nucleophilicity of thiocarboxylate ions,[3] it is surprising that the thioacid analogue of Mosher's acid has not previously been reported.[4] We have found that thioacid **3**, referred to here as Mosher's thioacid, is readily prepared and easily forms stable salts with organic bases. Unlike salts of Mosher's acid, the thioacid salts are powerful nucleophiles, useful for accurately detecting the ee of small amounts of chiral S_N2-reactive compounds, possibly not thermally stable or readily resolved by chiral chromatography.

Mosher's thioacid, **3**, can be prepared by treating the acid chloride, **2**, with hydrogen sulfide.[5] But this approach is not convenient for a laboratory synthesis. Shin and Quinn[6] describe the preparation of fatty thioacids from fatty acid chlorides using thioacetic acid as a convenient carrier of hydrogen sulfide. This method (Scheme 1) gives a practical laboratory synthesis of Mosher's thioacid, which easily operates even on very small scale. Workup using an excess of aqueous ammonia[3a] and then acid produces optically active Mosher's thioacid with retention of configuration and high chemical and optical purities in high yield.[7]

The nucleophilicities of thioacids ($pK_a \approx 3.5$) are activated by conversion to their salts, thiocarboxylate ions. We have found that either the racemic or resolved salts, **5**, of Mosher's thioacid neutralized with Proton Sponge [1,8-bis(dimethylamino)naphthalene, Scheme 2] are readily recrystallized from minimal ethanol producing colorless shiny non-hygroscopic crystals that are remarkably stable in air and soluble in chloroform-*d* and many other organic solvents.[8]

In general, even as a dilute solution in chloroform, the thiocarboxylate anion of **5** is highly reactive in S_N2 reactions. Because S_N2 reactions normally occur with clean inversion at the reaction center, resolved **5** can provide information about the configuration and enantiomeric excess of chiral substrates.



Scheme 1. Synthesis of Mosher's thioacid, **3**.

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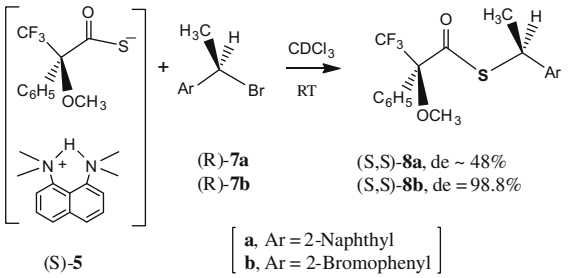
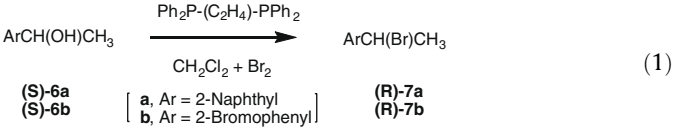


Scheme 2. Reactions of benzylic bromides with (*S*)-**5**.

As an indication of the range of reactivity of thiocarboxylate **5**, the following examples (collected in Table 1) show reactions with different S_N2 substrates. These range from more sluggish unactivated primary and secondary alkyl halides to much more reactive benzylic halides. On an approximate scale of S_N2 reactivities,[9] many classes of substrates normally exhibit intermediate reactivities and are also expected to show reactivities that are suitable. These classes include, for example, primary and secondary halides on sp^3 carbons that are allylic, propargylic or alpha to carbonyl, ether or amine groups.

Initially we chose to study the reactions of **5** with optically active benzylic bromides. Fortuitously, this turned out to be a good choice because these substrates appear to define the upper limit of reactivity for clean S_N2 reactions. Also, this demonstrated that reagent **5** is excellent for detecting subtle differences in similar substrates.

Benzylic bromides **7a** and **7b** were prepared from the (*S*)-benzylic alcohols **6** by the diphos bromide method (Eq. 1).[10]



(1)

These benzylic bromides react with (*S*)-**5** as dilute solutions in $CDCl_3$ at room temperature to cleanly produce S_N2 products, the benzylic thioesters **8** (Scheme 2 and Table 1 entries 1-1 and 1-4). Elimination side reactions are insignificant and racemization is minimal, especially in the early stages of these reactions.[11] Monitoring by NMR[12] or GC[13], reagent (*S*)-**5** readily determined the ee of benzylic bromides **7** from the diastereomeric excess (de) of the thioester products, **8**.[14]

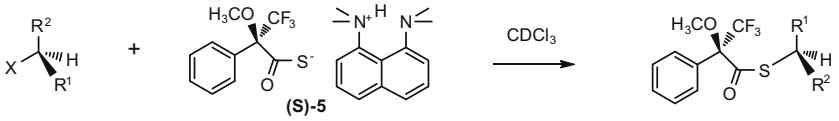
This analysis showed a surprising result. The de for each of the two thioester products **8** was dramatically different. Both benzylic bromides **7a** and **7b** were prepared from the corresponding (*S*)-alcohols of high optical purity. Both preparations used conditions essentially identical to those described by Stein.[10] The results show two very different ee values for the similar bromides **7a** and **7b**. At least in our hands, the stereochemical integrity of Stein's method differed markedly even in these two closely related cases: clean inversion for **7b** (entry 1-4) and major racemization for **7a** (entry 1-1). This difference was readily detected by reagent (*S*)-**5**.[15]

S_N2 reactions of **5** with even more reactive benzylic methanesulfonate esters (entry 1-2) and also reaction (of **3**) with benzylic alcohols activated under Mitsunobu conditions[16] (entry 1-3) are compromised by competing reactions and racemization. This was apparent from the time course of these reactions followed by GC and NMR analyses: the de of thioester products **8** decreased significantly as these reactions proceeded.[11b]

Unactivated alkyl halides and methanesulfonate esters are much less reactive S_N2 substrates than benzylic bromides.[9] Surprisingly, the thiocarboxylate anion of **5** remains quite S_N2-reactive with even unactivated secondary alkyl iodides. Unactivated bromides and methanesulfonate esters are considerably less reactive. Chlorides are nearly inert (see Table 2).[8c] This order of reactivity suggests an effect of hard and soft acid/base interactions.

The methanesulfonate esters of the chiral alcohols (*R*)-2-butanol and (*S*)-2-methyl-1-butanol were prepared (Scheme 3). Reaction of (*R*)-2-butyl methanesulfonate with (*S*)-**5** proceeded slowly

Table 1
Reaction of thiocarboxylate (*S*)-**5** with various chiral S_N2 substrates in $CDCl_3$ at rt



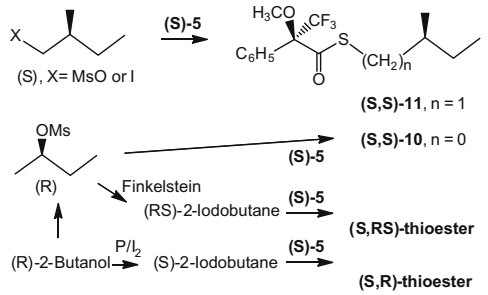
Entry	R^1	R^2	Substrate reacted with (*S*)-**5**					Primary S_N2 product	
			X	Preparation[a]	Precursor[b]	$[\alpha]_D$	Stereochem	Stereochem	de (%)
1-1	CH_3	2-Naphthyl	Br	1	(*S*)-Alc	~+23	(*R*)	(*S*,*S*)	⩾47[c], ⩾48[d]
1-2	2-Naphthyl	CH_3	OMs	2	(*S*)-Alc	—	(*S*)	(*S*,*R*)	85–95[c,e,f]
1-3	2-Naphthyl	CH_3	Mit.[g]	3	(*S*)-Alc	—	(*S*)	(*S*,*R*)	94[d,f]
1-4	CH_3	2-Bromophenyl	Br	1	(*S*)-Alc	−48	(*R*)	(*S*,*S*)	98.8[d]
1-5	(*S*)-2-Methylbutyl	H	I	4	(*S*)-Ms	+5.5, neat	(*S*)[n]	(*S*,*S*)	90–100[h,i]
1-6	CH_3	C_2H_5	OMs	5	(*R*)-Alc	—	(*R*)	(*S*,*S*)	94[i,j,k]
1-7	CH_3/C_2H_5	C_2H_5/CH_3	I	4	(*R*)-Ms	—	(*RS*)	(*S*,*RS*)	~0[i,j,l]
1-8	C_2H_5	CH_3	I	6	(*R*)-Alc	+20, neat	(*S*)	(*S*,*R*)	50[m]

[a] Substrate preparation conditions: (1) Diphos., $2Br_2$, 0 °C, CH_2Cl_2; (2) $MsCl/Et_3N$, 0 °C, THF; (3) Mitsunobu, $CDCl_3$; (4) NaI, acetone, Δ; (5) $MsCl/Et_3N$, 0 °C, CH_2Cl_2; (6) P/I_2, neat, Δ.
[b] Substrate precursor stereochemistry: Alc = alcohol, Ms = mesylate.
[c] By ^{19}F NMR.
[d] By GC/MS.
[e] Extrapolated to $t = 0$ to minimize effects of competing racemization.
[f] Significant unidentified reactions interfered.
[g] Mitsunobu-activated complex.
[h] Estimated by ^1H NMR, which is poorly resolved.
[i] S_N2 reaction was run as a highly concentrated solution.
[j] By FID-GC.
[k] The starting (*R*)-2-butanol is about 95% optically pure.
[l] The starting (*R*)-2-butyl methanesulfonate has ee 94%—see entry 1-6.
[m] The ee for precursor (*S*)-2-iodobutane was 50% by chiral GC.
[n] Stereochemistry is not altered.

Table 2
S_N2 chemistry of **5** in $CDCl_3$ with achiral substrates

Substrate	Result[a]
n-$C_6H_{13}Cl$	Large excess → slow pseudo first order reaction kinetics, $t_{1/2}$ ~22 h at 37 °C
$(CH_3)_2CHCl$	No reaction even in large excess
$C_2H_5OCH_2Cl$	Rapid S_N2 reaction. Can be used to quench **5**
CH_2Cl_2	Slow sequential reactions (→diastereomers)
$CDCl_3$	No reaction
CH_3I	Rapid S_N2 reaction. Can be used to quench **5**

[a] Room temperature, except for first entry.



Scheme 3. Reactions of (*S*)-**5** with unactivated substrates.

but smoothly in $CDCl_3$ and indicated that the optical purity of the starting alcohol (ca. 95%) was preserved (entry 1-6). Both methanesulfonate esters were then converted to the corresponding alkyl iodides using Finkelstein conditions. As is expected, the reaction of (*S*)-**5** with (*S*)-2-methyl-1-iodobutane, where the S_N2 reaction center is adjacent to the chiral center, showed that the integrity of the (*S*)-center was preserved (entry 1-5).

In marked contrast, the reaction of thiocarboxylate (*S*)-**5** with 2-iodobutane prepared from the (*R*)-methanesulfonate ester (entry 1-7) clearly indicated that this iodide was racemic—racemized by the standard Finkelstein reaction conditions.

That reagent (*S*)-**5** successfully detected the optical purity of 2-iodobutane was demonstrated by reaction with (*S*)-2-iodobutane prepared otherwise[17] (entry 1-8). In this case polarimetry failed to determine the ee of 2-iodobutane.[18] However, chiral GC did successfully separate the enantiomers[19] and confirm the results obtained with (*S*)-**5**.

Further observations on the reactivities of **5** are shown in Table 2. 1-Chlorohexane, in high excess, reacts only slowly following pseudo first order kinetics. Chloroform and 2-chloropropane are essentially inert. Dichloromethane, however, is slowly reactive and proceeds to mono and disubstituted products at long reaction times. At the opposite extreme, methyl iodide and chloromethyl ethyl ether react rapidly and can be used to quench the reactions of **5**.

In conclusion, salts of Mosher's thioacid, (*S*)-**3**, and in particular the salt (*S*)-**5** formed with Proton Sponge, are effective nucleophiles that cleanly react with S_N2 substrates ranging in reactivities from unactivated alkyl bromides, iodides, and mesylates to benzylic halides. We expect that Mosher's thioacid and corresponding salts will find a wide range of uses.[20]

Acknowledgments

The author thanks Professor Larry P. Wackett for his support during the course of this work. Inspiration came from Professor D. Y. Curtin (University of Illinois) and (for sulfur chemistry) from early work done in the laboratory of the late Professor William E. Truce at Purdue University.

Supplementary data

Supplementary data (experimental details, the IR spectra and ^1H, ^{19}F, and ^{13}C NMR spectra for **3** and **5**, and representative NMR spectra for **8**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.041.

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7. Details for preparation and properties of (*S*)-**3** [90% yield from (*R*)-**1**] and comments about (*RS*)-**3**, (*RS*)-**5** and (*R*)-**5** are presented in the Supplementary data.
8. (a) Elemental analyses (C, H, N, S) were acceptable (±0.3%) after a single recrystallization; (b) salts **5** are moderately photolabile; (c) dichloromethane reacts slowly.
9. For an approximate scale of reactivities of S_N2 substrates, see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley: New York, 2001, p 439.
10. Stein, A. R. *Can. J. Chem.* **1994**, *72*, 1789–1796.
11. (a) A comparison with the much less reactive Na^+ salt of Mosher's acid is given in the Supplementary data; (b) methodologies described in the Supplementary data and note 13 below minimize effects of racemization and compensate for kinetic sorting and detector response factors.
12. *Short approximate NMR analysis of* **7b**: 6.7 mg (14 μmol) of (*S*)-**5** and 3.5 mg (13 μmol) of (*R*)-**7b** in 0.75 mL of $CDCl_3$ showed no remaining **7b** after 6 days (rt). ^{19}F NMR integration of singlets for (*S*,*S*)- and (*S*,*R*)-**8b** at −69.49 and −69.30 ppm show the de ~96%. More accurate GC integrations, uncorrected for differences in detector response, show de ⩾ 93.4. Racemization, especially near completion, sets the lower limit to de.
13. *Accurate GC analysis of* **7b**: A mix of 1.8 mg (7 μmol) of (*R*)-**7b** and 7.5 mg (16.1 μmol) of (*S*)-**5** in 0.1 mL $CDCl_3$ was quenched (CH_3I) 2 min after mixing (rt). GC shows de = 98.5%, but this result is not corrected for kinetic sorting and detector response factors. GC analysis of an analogous experiment using (*RS*)-**7b** and (*S*)-**5** (or vice versa) shows the diastereomeric ratio [(*S*,*S*)/(*S*,*R*)] is 0.80 indicating that the corrected de above is 98.8% early in the reaction when racemization is insignificant.
14. (a) Assigning the ee value for the substrate (**7**) as being equivalent to the de values of substitution products (**8**) rests on the assertion that the ee of the nucleophile is high (>>99%) and that the stereointegrity of the S_N reactions and the stereo stabilities of the reactants and products are high; (b) the configuration of the α-carbon of Mosher's acyl group is listed first followed by the configuration of the thiol chiral carbon.
15. Confirmation of the low optical purity of benzylic bromide **7a** came from two additional observations. First, recrystallization of **7a** of optical rotation +23 (first preparation) or +37 (second preparation) increased the rotation to a maximum value of +64.3. Analysis of this purified **7a** by reaction with (*S*)-**5** indicated that the ee still had not reached 100%, only 94%. Second, another derivative, benzyl 1-(2-naphthyl)ethyl sulfide (**9**, reported by Givens, et al. *J. Am. Chem. Soc.* **1984**, *106*, 1779–1789), was prepared from **7a** of optical rotation +23. On recrystallization, the optical rotation of **9** increased 2.36 times. Both these polarimetry results indicate that the initial ee of **7a** was low, approximately 0.4 but are lower limits set by the unknown purities for both crude **7a** and **9**. Note also that observations reported in the Supplementary data indicate that both (*RS*)-**7a** and **9** are examples of racemic conglomerates. See Ref. 2a, p 7.
16. See, for a closely related example: Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119–3122.
17. (a) Kornblum, N.; Patton, J. T.; Nordmann, J. B. *J. Am. Chem. Soc.* **1948**, *70*, 746–749; (b) Clarke, L. *J. Am. Chem. Soc.* **1908**, *30*, 1144–1151.
18. Results suggesting that $[\alpha]_D^{27}$ +40 for optically pure (*S*)-2-iodobutane are presented in the Supplementary data.
19. Chiral GC on 2-iodobutane: Miranda, E.; Sanchez, F.; Sanz, J.; Jimenez, M. I.; Martinez-Castro, I. *J. High Resolut. Chromatogr.* **1998**, *21*, 225–233. Note also

that GC separation of the (*S*,*R*)- and (*S*,*S*)-thioesters of **10** [prepared from the (*RS*)-thiol] was previously reported: Kukula, P.; Dutly, A.; Sivasankar, N.; Prins, R. *J. Catal.* **2005**, *236*, 14–20.

20. Claims to Mosher's thioacids, their salts, and related compounds are pending in US Patent Application 2009/0181462, by Jack E. Richman [*Chem. Abstr.* *151*: 173065 (2009)]. This patent position is not intended to restrict noncommercial research use, but will be used to preclude gifts, purchases, sales or commercial use of the compounds by anyone other than authorized licensees.