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Synthesis of α-Chloroaldoxime *O*-Methanesulfonates and Their Use in the Synthesis of Functionalized Benzimidazoles

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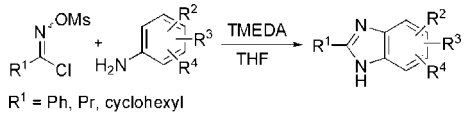
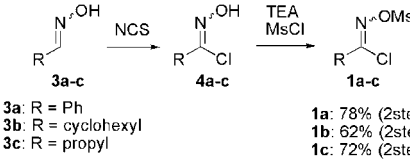
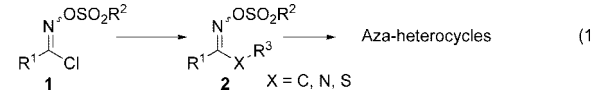


Three different α-chloroaldoxime *O*-methanesulfonates were synthesized to investigate their chemical properties. The compounds were found to be stable and were able to be stored at ambient temperature without any precautions. The reactions with anilines were investigated, and it was found that an additive is required to activate the sulfonate. TMEDA was found to be the most efficient additive, and various benzimidazoles were synthesized through the reaction.

Synthesis of new reagents and their application to synthesis of functionalized heterocycles are of great interest in organic synthesis, as such motifs are ubiquitous in both natural products and biologically active pharmaceutical agents. Development of such reagents is extremely important, not only because it provides a more practical pathway to highly functionalized heterocycles, but also because it could enable one to synthesize new heterocycles that are difficult to synthesize by conventional methodologies. We became particularly interested in the synthesis of α-chloro oxime *O*-sulfonates **1** and their chemical properties, since these compounds should allow one to easily synthesize *O*-sulfonyl oximes **2** which are frequently used for the synthesis of aza-heterocycles (eq 1).[1] Despite the significant synthetic potential of these compounds, less attention has been received. Few examples exist for the synthesis of these compounds,[2] and only one synthetic application had appeared in the literature, that is to synthesize 1,4,2-dithiazolium salt.[3] This is plausibly due to the lack of general information of the chemical properties (stability, reactivity, etc.) of these compounds. We envisioned that further study of this class of compound would make us realize the full potential of this class of compounds, and thus lead to a discovery of new chemistry. We report herein a practical method to access α-chloroaldoxime *O*-methanesulfonate **1a**−**c** (Scheme 1), and the first extensive studies on the reactivity toward anilines, with an aim to obtain benzimidazoles.[4,5]

SCHEME 1. Synthesis of α-Chloroaldoxime *O*-Methanesufonates





α-Chloroaldoxime *O*-methanesulfonates bearing a phenyl group (**1a**), a cyclohexyl group (**1b**), and a propyl group (**1c**) were synthesized from the corresponding aldoxime (Scheme 1). All of the compounds were stable through aqueous workup, and were able to be purified through silica gel column chromatography. α-Chlorobenzaldoxime *O*-methanesufonate **1a** was obtained as a white crystalline solid, where α-chlorocyclohexanecarboxaldoxime *O*-methanesufonate **1b** and α-chlorobutylaldoxime *O*-methanesufonate **1c** were obtained as colorless oils. Importantly, all of the compounds were stable for more than a month at ambient temperature without any precautions.

The reaction between α-chlorobenzaldoxime *O*-methanesulfonate **1a** and *p*-methoxyaniline **5a** was selected as a model reaction to investigate the best reaction conditions (Table 1). In this reaction, 5-methoxy-2-phenyl-1*H*-benzimidazole **7aa** is expected to be obtained through nitrene precursor **6**.[6] We first conducted the reaction in the presence of TEA, but no reaction occurred even at elevated temperature (entry 1). Deprotonation

(1) For review, see: (a) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505–4519. For recent advances in this area, see: (b) Feng, L.; Kumar, D.; Kerwin, S. M. *J. Org. Chem.* **2003**, *68*, 2234–2242. (c) Zaman, S.; Kitamura, M.; Abell, A. D. *Org. Lett.* **2005**, *7*, 609–611. (d) Szczepankiewicz, B. G.; Rohde, J. J.; Kurukulasuriya, R. *Org. Lett.* **2005**, *7*, 1833–1835. (e) Sadaoka, K.; Mihara, J.; Ichikawa, J. *Chem. Commun.* **2005**, 4684–4686. (f) Wahyuningshih, T. D.; Pchalek, K.; Kumar, N.; Black, D. StC. *Tetrahedron* **2006**, *62*, 6343–6348. (g) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021–1023. (h) Yamamoto, Y.; Tsuritani, T.; Mase, T. *Tetrahedron Lett.* **2008**, *49*, 876–878. (i) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918–6919.

(2) (a) Truce, W. E.; Naik, A. R. *Can. J. Chem.* **1966**, *44*, 297–305. (b) Rajagopalan, P.; Talaty, C. N. *Tetrahedron Lett.* **1966**, *19*, 2101–2108.

(3) (a) Florence, S.; Chan, Y.; Sammes, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 899–906. (b) Florence, S.; Chan, Y.; Sammes, M. P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 899–906.

(4) Partridge, M. W.; Turner, H. A. *J. Chem. Soc.* **1958**, 2086–2092. Also see ref 1h.

(5) For recent studies on the synthesis of benzimidazoles, see: (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133–136. (b) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598–2601. (c) Zheng, N.; Anderson, K. W.; Huang, X.; Nguyen, H. N.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7509–7512. (d) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932–1934. (e) Shen, M.; Driver, T. G. *Org. Lett.* **2008**, *10*, 3367–3370. (f) Yang, D.; Fu, H.; Hu, L.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 7841–7844.

(6) (a) Grenda, V. J.; Joens, R. E.; Gal, G.; Sletzinger, M. *J. Org. Chem.* **1965**, *30*, 259–261. (b) Sauer, J.; Mayer, K. K. *Tetrahedron Lett.* **1968**, *9*, 325–330. (c) Garapon, J.; Sillion, B.; Bonnier, J. M. *Tetrahedron Lett.* **1970**, *11*, 4905–4908. (d) Houghton, P. G.; Pipe, D. F.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1471–1479. (e) Ichikawa, M.; Hisano, T. *Chem. Pharm. Bull.* **1982**, *30*, 2996–3003. (f) Ramsden, C. A.; Rose, H. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 615–617. (g) Ramsden, C. A.; Rose, H. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2319–2327, and references cited therein.

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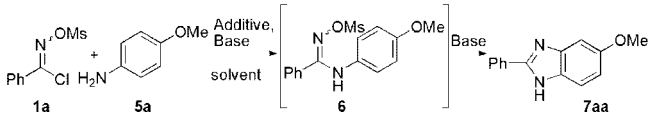
TABLE 1. Optimization of Reaction Conditions



entry	additive (equiv)	base (equiv)	solvent	temp, °C	yield,[a] %
1		TEA (2.2)	DMF	85	<5
2		NaH (2.2)	DMF	85	<5
3	DMAP (1.1)	TEA (2.1)	DMF	50	18
4	imidazole (1.1)	TEA (2.1)	DMF	50	36
5		Me_2NEt (2.1)	DMF	rt	72
6		TMEDA (2.1)	DMF	rt	76
7		TMEDA (2.1)	DMF	50	96
8		TMEDA (1.2)	DMF	50	92
9		TMEDA (2.1)	THF	50	87
10		TMEDA (2.1)	MeCN	50	63
11		TMEDA (2.1)	$CHCl_3$	50	87
12		TMEDA (2.1)	toluene	50	55

[a] HPLC yield.

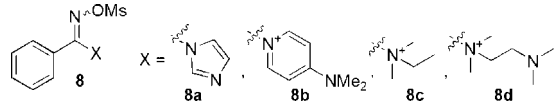


FIGURE 1. Plausible reactive intermediates.

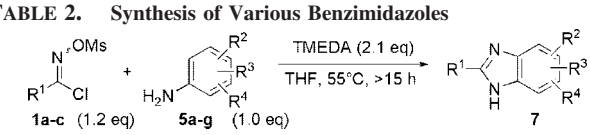
of aniline with NaH was also not effective (entry 2), and gave a complex mixture at 85 °C. We next turned our attention to activating the chloride **1a**, and soon found that the activation is possible by employing imidazole (entry 3) or DMAP (entry 4) to the reaction. The intermediate **8** (Figure 1)[7] formed immediately after the addition of the additives to the chloride **1a**, and slowly reacted with the aniline **5a** to give benzimidazole **7aa**, albeit in low yield. Further exploration revealed that the activation is also possible by an addition of a less sterically hindered base such as Me_2NEt or TMEDA,[8] which dramatically increased the yield. TMEDA was chosen for further investigation because of the volatility of Me_2NEt at higher temperature. DMF, THF, and $CHCl_3$ (entries 7, 9, and 11) were found to be suitable solvents for the reaction, but solvents such as MeCN and toluene (entries 10 and 12) resulted in low yield due to low conversion.

Having established optimized reaction conditions, reactions of three α-chloroaldoxime *O*-methanesulfonates **1a**−**c** with various anilines were investigated (Table 2). The reactions were conducted in THF in the presence of 2.1 equiv of TMEDA, and were stirred at 50 °C overnight. Among the three α-chloroaldoxime *O*-methanesulfonates **1a**−**c**, the reactivity of α-chlorocyclohexanecarboxaldoxime *O*-methanesulfonate **1b** was the lowest (entry 5 vs entries 1 and 10, entry 6 vs entries 2 and 11), which is plausibly due to the bulkiness of the cyclohexyl group. The reaction was also sensitive to the steric bulk at the ortho position of anilines (entry 2 vs 3), and reaction with anilines possessing ortho substituents resulted in low yield (entries 3, 14, and 15). Reaction with 4-substituted anilines generally gave the corresponding benzimidazoles in good yields, and functional groups such as ester (entry 4), MeS (entries 8 and 12), benzyloxy (entry 9), fluoro (entry 13), and iodo (entry 16) were all tolerated under these reaction conditions.

In summary, we have synthesized three different α-chloroaldoxime *O*-methanesulfonates to investigate the chemical properties of these compounds. The compounds were found to be stable, and thus required activation to react with anilines. TMEDA was found to be the best additive for the activation, and the reactions with various anilines were conducted to obtain numerous 2-substitued benzimidazoles. Further utilization of the α-chloroaldoxime *O*-methanesulfonates for the synthesis of heterocycles is currently under investigation in our laboratories.

(7) Not isolated, but determined by LCMS.
(8) In this case, no intermediates were observed by LCMS.

TABLE 2. Synthesis of Various Benzimidazoles



entry	chloride	aniline	Product	yield (%)
1	1a	5a	7aa	87
2	1a	5b	7ab	86
3	1a	5c	7ac	38
4	1a	5d	7ad	51
5	1b	5a	7ba	46
6	1b	5b	7bb	26
7	1b	5e	7be	11
8	1b	5f	7bf	8
9	1b	5g	7bg	20
10	1c	5a	7ca	85
11	1c	5b	7cb	95
12	1c	5f	7cf	57
13	1c	5h	7ch	92
14	1c	5i	7ci	54
15	1c	5j	7cj	10
16	1c	5k	7ck	12

Experimental Section

General Procedures for Synthesis of α-Chloroaldoxime *O*-Methanesulfonates (1a−c) from Their Corresponding Oximes: Representative Procedure for the Synthesis of 1a. To a 500 mL round-bottomed flask was added benzaldoxime (25 g, 206 mmol),

DMF (25 mL), THF (188 mL), and $CHCl_3$ (188 mL). A portion of NCS (2.89 g, 21.7 mmol, 0.105 equiv) was added to the mixture, and the mixture was stirred vigorously. After confirming the start of the reaction by the rise in temperature (mixture becomes a blue solution), the remaining NCS (26.0 g, 195.3 mmol) was added in small portions while keeping the temperature around 40−45 °C. The reaction mixture was stirred for 1 h and was then quenched with water (188 mL). The aqueous layer was discarded and the organic layer was washed with water (188 mL). The organic layer was dried over Na_2SO_4, then concentrated under reduced pressure.

To the residue was added EtOAc (960 mL), and the resulting solution was cooled to 0 °C. TEA (63.2 mL, 453 mmol, 2.2 equiv) was added to the solution, and the mixture was stirred at the same temperature for 10 min to give a white slurry. MsCl (26.0 g, 227 mmol, 1.1 equiv) was added, slowly over 10 min, to the mixture, and the mixture was warmed to room temperature. The mixture was stirred at room temperature for 1 h, and the crystal was filtered off. The filtrate was washed with H_2O (2 × 160 mL), dried over Na_2SO_4, and concentrated under reduced pressure, then isolated as a crystal from EtOAc.

α-Chlorobenzaldoxime *O*-Methanesulfonate (1a). Isolated as a crystal from EtOAc: 37.5 g (78% yield, 2 steps, mp 112−113 °C); TLC R_f 0.62 (EtOAc/hexanes, 1:4); FTIR (neat) υ_{max} 3050, 1560, 1377, 1319, 1259, 1180, 1155, 969, 892, 813, 771, 688, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 1H), 7.57 (m, 2H), 7.48 (m, 2H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5,132.5, 129.8, 128.2, 127.5, 36.3. Anal. Calcd for $C_8H_8ClNO_3S$: C, 41.12; H, 3.45; N, 5.99. Found: C, 41.27; H, 3.42; N, 5.88.

General Procedures for Synthesis of Benzimidazoles from Aniline and α-Chloroaldoxime *O*-Methanesulfonates: Representative Procedure for the Synthesis of 7aa. To a 50 mL round-bottomed flask was added *p*-anisidine (369 mg, 3 mmol), α-chlorobenzaldoxime *O*-methanesulfonate **1a** (841 mg, 3.6 mmol), THF (3.7 mL), and TMEDA (0.95 mL, 6.3 mmol). The solution was warmed to 50 °C and then stirred for 15 h. The mixture was quenched with water and extracted with EtOAc. The aqueous layer was discarded and the organic layer was dried over Na_2SO_4 and evaporated. The residue was purified through a SiO_2 column to give benzimidazole **7aa** as a white crystal (585 mg, 87% yield).

5-Methoxy-2-phenyl-1*H*-benzimidazole (7aa) Mixture of Tautomers. Isolated as a white crystal (87% yield, mp 149−150 °C): TLC R_f 0.36 (EtOAc/hexanes, 1:1); FTIR (neat) υ_{max} 3055, 2931, 1631, 1456, 1404, 1269, 1159, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.7 (s, 0.45H), 12.7 (s, 0.55H), 7.24−7.54 (m, 4H), 7.18 (br s, 0.45H), 6.98 (br s, 0.55H), 6.80−6.86 (m, 1H), 3.80 (s, 1.65H), 3.78 (s, 1.35H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.3, 155.6, 151.6, 150.5, 144.8, 138.5, 135.8, 130.5, 129.6, 129.0, 126.3, 120.0, 112.4, 111.7, 111.3, 101.5, 94.6, 55.6; HRMS *m*/*z* calcd for $C_{14}H_{12}N_2O$ 224.0950, found 224.0952.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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