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Reactions of Oxetan-3-*tert*-butylsulfinimine for the Preparation of Substituted 3-Aminooxetanes

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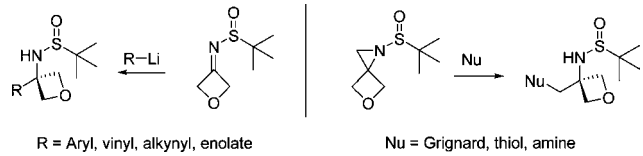
ABSTRACT



The oxetane ring is useful in drug discovery as a bioisostere for both the geminal dimethyl group and the carbonyl group. A convenient, straightforward approach to access structurally diverse 3-aminooxetanes through the reactivity of oxetan-3-*tert*-butylsulfinimine and the corresponding sulfinylaziridine is described.

The replacement of a geminal dimethyl group with an oxetane ring is a potentially useful exercise in drug discovery.[1] Although presenting a similar van der Waals volume to a geminal dimethyl group, an oxetane ring can be more stable to oxidative metabolism and exhibit decreased lipophilicity, two properties that can confer an enhanced pharmacokinetic profile.[1a] The decreased lipophilicity can also mitigate undesirable off-target effects, such as hERG channel binding[2] and hPXR activation.[3] Additionally, studies suggest that an oxetane ring can also act as a stable surrogate for the carbonyl group; both groups have similar hydrogen-bond basicity,[4] but oxetanes do not have the same electrophilic reactivity or susceptibility toward α-epimerization of stereocenters.[1b]

During the course of a medicinal chemistry program, we became interested in preparing a 3-aryl-3-aminooxetane (Figure 1) in order to examine the possibility of replacing

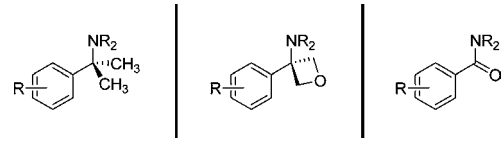


Figure 1. Oxetanes as potential bioisosteres for the geminal dimethyl or carbonyl group.

the dimethyl group in a key pharmacophore for the reasons outlined above. At the time, we found no reports of this structural motif, which was surprising given the apparent low degree of structural complexity.[5]

(1) (a) Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736–7739. (b) Wuitschik, G.; Rogers-Evans, M.; Buckl, A.; Bernasconi, M. M.; Godel, T.; Holger, F.; Wagner, B.; Parilla, I.; Schuler, F.; Schneider, J.; Alker, A.; Schweizer, W. B.; Müller, K.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512–4515.

(2) (a) Fermini, B.; Fossa, A. *Nat. Rev. Drug Discovery* **2003**, *2*, 439–447. (b) Jamieson, C.; Moir, E. M.; Rankovic, Z.; Wishart, G. *J. Med. Chem.* **2006**, *49*, 5030–5046.

(3) (a) Ngan, C.; Beglov, D.; Rudnitskaya, A. N.; Kozakov, D.; Waxman, D. J.; Vajda, S. *Biochemistry* **2009**, *48*, 11572–11581. (b) Gao, Y.-D.; Olson, S. H.; Balkovec, J. M.; Zhu, Y.; Royo, I.; Yabut, J.; Evers, R.; Tan, E. Y.; Tang, W.; Hartley, D. P.; Mosley, R. T. *Xenobiotica* **2007**, *37*, 124–138.

(4) (a) Berthelot, M.; Besseau, F.; Laurence, C. *Eur. J. Org. Chem.* **1998**, 925–931. (b) Besseau, F.; Lucon, M.; Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 101–107.

(5) During the preparation of this manuscript, a related report was published in the patent literature: Rainer, A.; Cooke, N. G.; Zecri, F.; Lewis, I. International Patent Application WO 2009/068682 A2, June 4, 2009.

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One attractive approach to the synthesis of 3-aryl-3-aminooxetanes involved the 1,2-addition of an arylmetal nucleophile into an activated oxetan-3-imine, as it could potentially allow for the modular, late-stage introduction of the oxetane ring onto an appropriate aryl building block (Figure 2). We chose to utilize Ellman's *tert*-butylsulfinimine

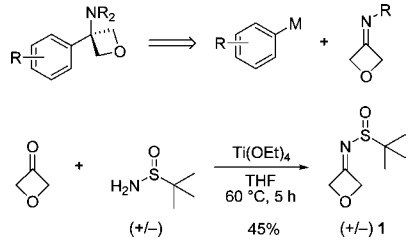


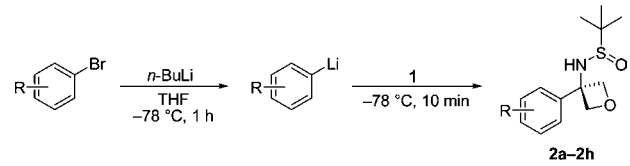
Figure 2. Retrosynthesis of 3-aryl-3-aminooxetanes, and preparation of sulfinimine **1**.

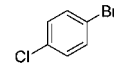
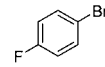
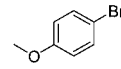
chemistry because of the availabilty of 2-methyl-2-propane-sulfinamide, the well-studied reactivity of *tert*-butylsulfinimines, and the ease of removal of the *tert*-butylsulfinyl group to provide the deprotected amines.[6]

Condensation of commercially available oxetan-3-one with racemic 2-methyl-2-propane-sulfinamide at 60 °C, utilizing titanium(IV) ethoxide as a dehydrating reagent,[6a] provided oxetan-3-*tert*-butylsulfinimine (**1**) as a slightly volatile oil.[7] With access to sulfinimine **1**, we began to explore its reactivity toward organometallic reagents. Phenyllithium underwent 1,2-addition to **1** at −78 °C in tetrahydrofuran to give the *tert*-butylsulfinyl protected 3-phenyl-3-aminooxetane in 91% yield (Table 1, entry 1). It is noteworthy that the addition proceeds in high yield without the use of trimethylaluminum as a Lewis acid, as is typically required to enhance the yield in the addition of organolithium reagents to *N*-sulfinyl ketimines.[6c] We next examined several other phenyllithium reagents, including electron-deficient (Table 1, entries 2−5) and electron-rich (Table 1, entries 6−8) aromatic rings. The required aryllithium reagents were each generated by lithium−halogen exchange[8] of the corresponding bromides and underwent clean 1,2-addition to give products **2b**−**2h** in good to excellent yield.

Selective removal of the *tert*-butylsulfinyl group[6b] was accomplished in the presence of the potentially acid-labile oxetane ring by brief (1−5 min) treatment of a solution of **2a** in methanol at 0 °C with hydrochloric acid (4 N in

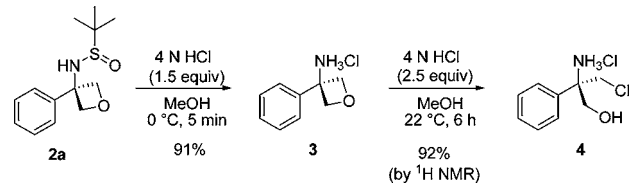
Table 1. Aryllithium Additions into **1** To Access Protected 3-Aryl-3-aminooxetanes



entry	aryl bromide	product	yield (%)
1		**2a**	91
2		**2b**	79
3		**2c**	83
4		**2d**	90
5		**2e**	77
6		**2f**	51
7		**2g**	57
8		**2h**	55

dioxane, 1.5 equiv) to give the pure hydrochloride salt of 3-phenyl-3-aminooxetane (**3**) in 91% yield after trituration with diethyl ether. Prolonged exposure to hydrochloric acid should be avoided, as the ring-opened chlorohydrin **4** begins to form (Scheme 1) under the deprotection conditions.[9]

Scheme 1. Removal of the *tert*-Butylsulfinyl Group To Give **3**



Although our initial goal was to prepare 3-aryl-3-aminooxetanes, we next decided to explore further the reactivity of sulfinimine **1** toward diverse nucleophiles for the preparation of a variety of 3-substituted-3-aminooxetanes. Several

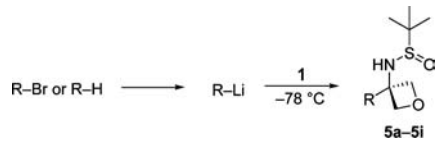
(6) (a) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. *J. Org. Chem.* **1999**, *64*, 1278–1284. (b) Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883–8904. (c) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268–269.

(7) Sulfinimine **1** was stable to chromatography on silica gel and benchstable at 22 °C for several weeks.

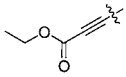
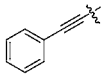
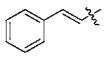
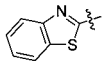
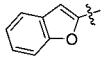
(8) (a) Wittig, G.; Pockels, U.; Droge, H. *Chem. Ber.* **1938**, *71*, 1903–12. (b) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106–109. For general reference, see: (c) Leroux, F.; Schlosser, M.; Zohar, E.; Marek, I. The preparation of organolithium reagents and intermediates. In *Organolithium Compounds*; Strasbourg, F., Ed.; John Wiley & Sons Ltd.: Chichester, U.K., 2004; Vol. 1, pp 435−493. (d) Wakefield, B. J. *Organolithium Methods*; Pergamon Press: New York, 1988. (e) Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1–46.

representative heterocycles bearing an acidic hydrogen were metalated with *n*-butyllithium, and the corresponding anions underwent 1,2-addition to **1** to generate **5f**−**5i** in excellent yield (Table 2, entries 6−9).

Table 2. Addition of Diverse Nucleophiles to **1** To Access Substituted 3-Aminooxetanes[a]



5a–5i

entry	R	conditions[a]	addition time	product	yield (%)
1		R–H, *n*-BuLi –78 °C 30 min	10 min	**5a**	62
2		R–H, *n*-BuLi –78 °C 10 min	30 min	**5b**	82
3		R–H, *n*-BuLi –78 °C 30 min	10 min	**5c**	80
4		R–Br, *t*-BuLi –78 → 22 °C 1 h	30 min	**5d**	67
5		R–H, LDA –78 °C 30 min	3 h	**5e**	91
6		R–H, *n*-BuLi –78 → 0 °C 1 h	15 min	**5f**	76
7		R–H, *n*-BuLi –78 → 0 °C 30 min	30 min	**5g**	82
8		R–H, *n*-BuLi –78 °C 30 min	30 min	**5h**	98
9		R–H, *n*-BuLi –78 °C 1 h	30 min	**5i**	78

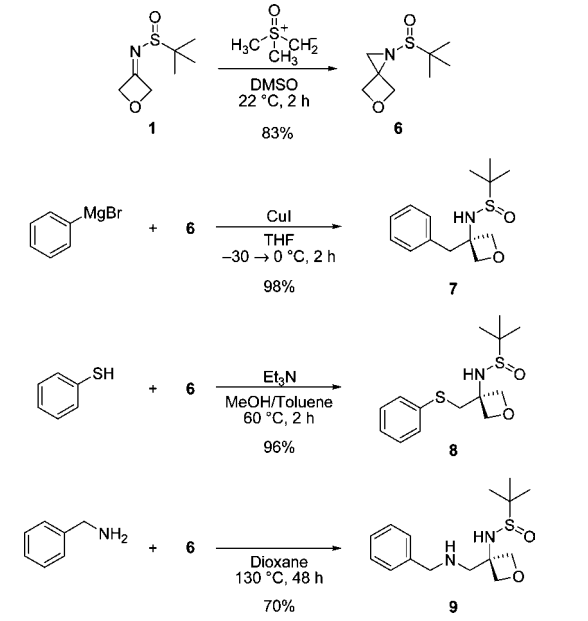
[a] Entries 1−3 and 5−9 performed in THF, entry 4 performed in 3:2 hexanes/diethyl ether.

Branching out from aryllithium substrates, we examined several classes of carbanions across a range of nucleophilicity. Ethyl propiolate, phenylacetylene, and trimethylsilylacetylene were deprotonated with *n*-butyllithium, and each of the corresponding anions added to **1** in good yield to give 3-alkynyl-3-aminooxetanes **5a**−**5c** in protected form[10] (Table 2, entries 1−3). The trimethylsilylacetylene adduct (**5a**) could be selectively deprotected to give either the free amine (HCl, MeOH, 0 °C, 1−5 min, 95%)[6b] or the free alkyne (K_2CO_3, $MeOH-CH_2Cl_2$, 5 min, 22 °C, 94%),[11] allowing selective elaboration of either the terminal alkyne[12] or amine functionality. Vinyllithium reagents[13] (Table 2, entry 4) also added to **1** efficiently, giving access to allylic aminooxetanes in good yield. Finally, lithium enolates[14] underwent addition to **1** in excellent yield to give β-(3-aminooxetane)-esters (Table 2, entry 5).

Primary alkyllithium reagents such as *n*-butyllithium and (2-phenylethyl)lithium[15] added to **1** in poor yield (17% and 18%, respectively). Attempts at optimizing the reaction conditions suggested that competitive deprotonation of the oxetane ring within **1** was a source of low conversion and side-products; conversion was not improved by the addition of excess *n*-butyllithium (4 equiv), and deuterium quench experiments indicated that **1** recovered from the reaction mixture was enriched in deuterium.[16]

Having explored the reactivity of **1** toward several classes of nucleophiles, we next examined the possibility of generating a sulfinylaziridine from sulfinimine **1**. Ring-opening reactions of a spiro-aziridine would expand the product scope to homologated 3-aminooxetanes. Treatment of sulfinimine **1** with dimethyloxosulfonium methylide[17] (DMSO, 22 °C, 2 h) generated the novel, highly strained aziridine **6** in 83% yield (Scheme 2).

Scheme 2. Synthesis and Ring-Opening Reactions of **6**



Aziridine **6** could be opened with phenylmagnesium bromide (promoted by CuI)[18] to give a benzyl substituted

(9) After 5 min at 22 °C, only the desired deprotected product was observed. However, after 30 min at 22 °C, the ratio of **3** to **4** was 85:15 by ^{1}H NMR, and after 6 h at 22 °C with 2.5 equiv of HCl, the ratio of **3** to **4** was 8:92.

(10) Representative deprotection of select examples can be found in Supporting Information.

(11) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 732–757.

(12) For example, the terminal alkyne could undergo cycloaddition with azides to give access to a triazole functionalized with a 3-aminooxetane; see Supporting Information for details.

(13) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847–853.

(14) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819–7832.

(15) Bailey, W. F.; Punzlan, E. R. *J. Org. Chem.* **1990**, *55*, 5404–5406.

3-aminooxetane (**7**) in excellent yield (98%). In addition to carbon-based nucleophiles, aziridine **6** could also be opened efficiently with sulfur-based[18] (thiophenol, triethylamine, 60 °C) and nitrogen-based[19] (benzylamine, 130 °C) nucleophiles, further expanding the product scope of this methodology for generating substituted 3-aminooxetanes.

In conclusion, we have described here the synthesis of oxetan-3-*tert*-butylsulfinimine (**1**) and demonstrated the utility of **1** in reactions with a variety of organolithium reagents for the straightforward synthesis of 3-aminooxetanes. As outlined above, the product 3-aminooxetanes are of general interest to medicinal chemists for use as bioisosteres for the geminal dimethyl group. We have also described the conversion of **1** to the novel sulfinylaziridine **6**, enabling access to an expanded product scope by ring-opening reactions of **6** with both carbon- and heteroatom-based nucleophiles.

Acknowledgment. Part of this work was completed as part of the Cooperative Education Program with Northeastern University, Boston, MA (P.J.H.). We thank our Merck colleagues Bridget Becker and Bruce Adams for assistance with NMR analysis, Charles W. Ross III for providing accurate mass measurement analysis, and Roy Helmy for determination of deuterium enrichment.

Supporting Information Available: Detailed experimental procedures, tabulated spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Recovered **1** was 50% mono-deuterated by MS analysis when **1** was treated with *n*-BuLi (1 equiv, −78 °C, 1 h), followed by addition of deuterated acetic acid at −78 °C.

(17) TMSOI: (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364. TMSOI in aziridinations: (b) Davis, F. A.; Zhou, P.; Liang, C.; Reddy, R. E. *Tetrahedron: Asymmetry* **1995**, *6*, 1511–1514.

(18) Hodgson, D. M.; Hughes, S. P.; Thompson, A. L.; Heightman, T. D. *Org. Lett.* **2008**, *10*, 3453–3456.

(19) Burgaud, B. G. M.; Horwell, D. C.; Padova, A.; Pritchard, M. C. *Tetrahedron* **1996**, *52*, 13035–13050.