Electrochemical Intramolecular Oxytrifluoromethylation of N -Tethered Alkenyl Alcohols: Synthesis of Functionalized Morpholines

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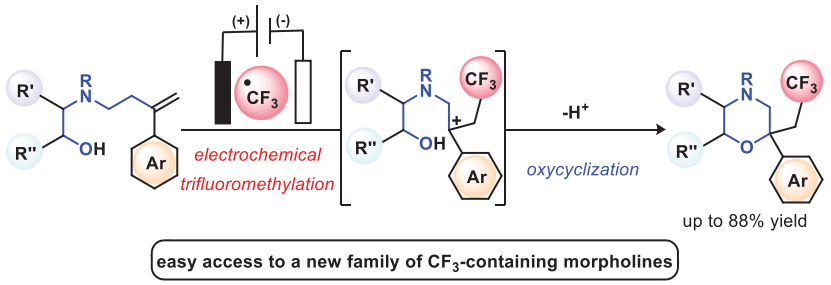
Supporting Information Placeholder

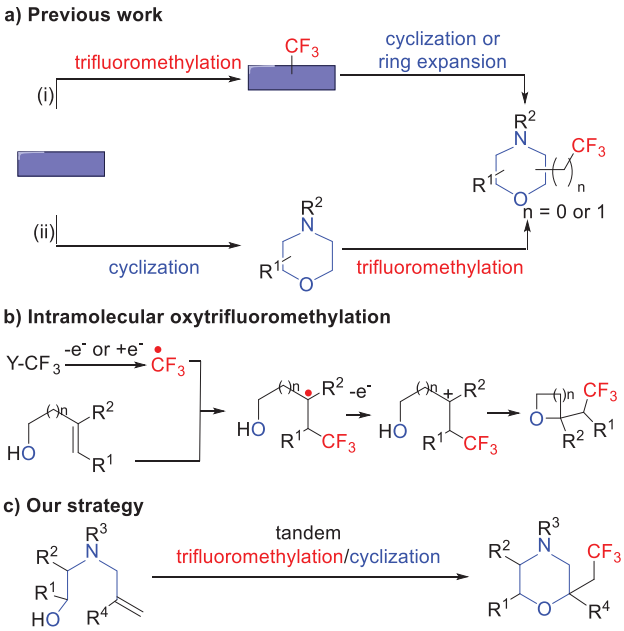


ABSTRACT: An electrochemical intramolecular oxytrifluoromethylation of *N*-tethered alkenyl alcohols was developed providing straightforward access to CF_3-containg morpholines derivatives. The method features mild reaction conditions with direct anodic oxidation of Langlois reagent as cheap and easy to handle trifluoromethylating reagent. Variously substituted 2-(2,2,2-trifluoroethyl)morpholines were obtained in moderate to high yields under constant current electrolysis in an undivided cell.

Tetrahydro-1,4-oxazines, namely morpholine derivatives, are privileged core skeletons that continually appear in numerous pharmaceuticals and agrochemicals.[1,2] It belongs to the top 25 most frequent *N*-heterocycles in US FDA approved drugs.[3] Recently, trifluoromethylated morpholines have received substantial interest because the incorporation of a trifluoromethyl (CF_3) group can significantly improve their physical, biological and chemical properties.[4] Therefore, several efficient methods have been developed to construct trifluoromethylated morpholines that rely on two main strategies (Scheme 1a). The first one involves the construction of the morpholine core *via* either cyclization of trifluoromethylated linear compounds[5] or the ring expansion of CF_3-containing heterocycles.[6] The second one is based on trifluoromethylation of existing morpholines.[7] Although both approaches have their own particular advantages, exploring more efficient synthetic methodologies for valuable trifluoromethylated morpholines is still highly desired.

Over past decades, the intramolecular difunctionalization of alkenes involving the simultaneous formation of C–CF_3 and C–O bonds has proven to be a powerful tool for synthesis of trifluoromethylated oxacycles.[8] This approach involves the generation of a CF_3 radical via a single-electron transfer (SET) process which reacts with an alkene to provide a β-CF_3-substituted radical intermediate. The resulting radical then undergoes a stepwise SET oxidation and subsequent intramolecular O-nucleophilic attack to produce oxygen-containing heterocycles (Scheme 1b). Surprisingly, to the best of our knowledge, such an intramolecular oxytrifluorometylation has not been investigated for the preparation of CF_3-containing morpholines. The development of such a cyclization reaction would provide an efficient synthesis of novel family of trifluoromethylated morpholines (Scheme 1c).

Scheme 1. Synthesis of CF_3-containing Morpholines

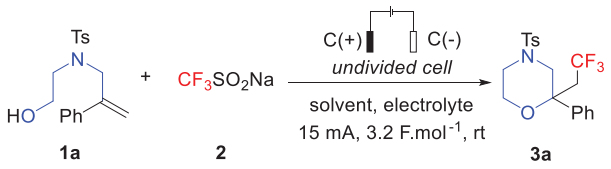


In recent years, electrochemistry[9] has emerged as a powerful tool to introduce a CF_3 group into alkenes[10] through the anodic oxidation of the cheap and easy to handle Langlois reagent (CF_3SO_2Na).[11,12] It has been applied for the construction of pyrrolidines,[13] oxindoles,[14] indoline or hydroisoquinoline-1,3-diones,[14b] quinolinones and lactones[8n] *via* intramolecular processes. In this context and in line with our long-standing interest in rad-

ical trifluoromethylation of alkenes,[15,8l] we speculated that electrochemical trifluoromethylation/cyclization of *N*-tethered alken-6-ols is a worthwhile approach to accessing trifluoromethylated morpholines. Herein we report our preliminary efforts toward the construction of new type of 2-(2,2,2-trifluoroethyl)morpholine derivatives.

Our investigations began by studying the cyclization of alken-6-ol **1a** with Langlois reagent **2** in an undivided cell using graphite carbon cathode, a platinum cathode under constant current electrolysis and a mixture of CH_3CN and H_2O (v/v 1:1) (Table 1). With $LiClO_4$ as the electrolyte, the desired morpholine **3a** was isolated in 62% yield (entry 1). After testing other organic solvents such as acetone and THF (entries 2 and 3), CH_3CN was considered to be the best one. Replacing H_2O by methanol had no significant effect. When the electrolysis was conducted in pure CH_3CN to reduce the formation of intermolecular oxytrifluoromethylated product,[16] **3a** was isolated with an improved yield of 79%. Pleasingly, switching platinum plated anode for cheap carbon graphite or nickel electrodes gave similar results (entries 6 and 7). Further experiments have shown that a change of the electrolyte or current intensity (from 15 to 30 mA) leads to a significantly decrease of yield (entries 8 and 9).[17]

Table 1. Optimization of Reaction Conditions[a]



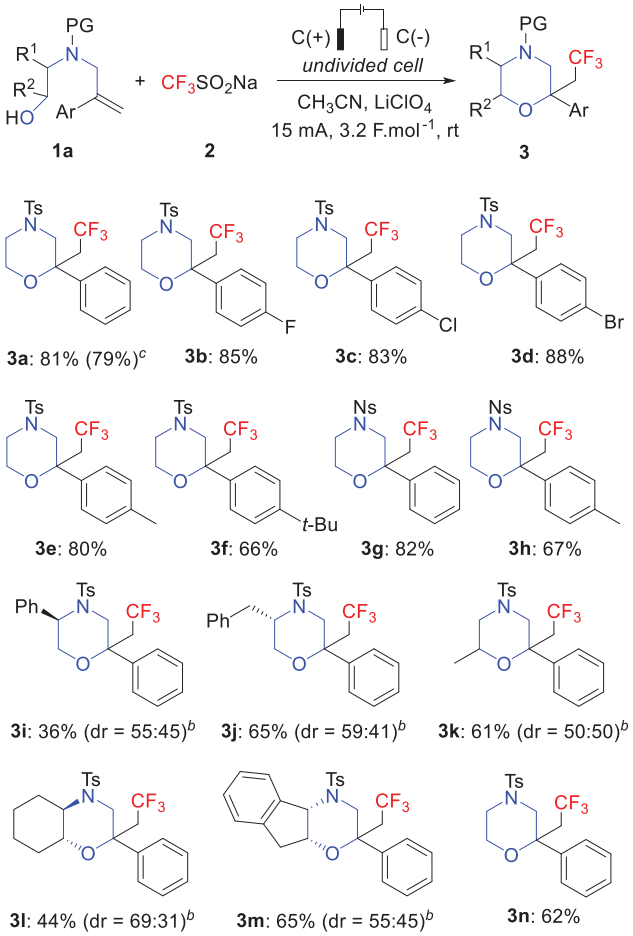
1a **2** **3a**

entry	electrodes	solvent	yield[b] (%)
1	C(+)|Pt(-)	CH_3CN/H_2O (10:1)	62
2	C(+)|Pt(-)	acetone/H_2O (10:1)	48
3	C(+)|Pt(-)	THF/H_2O (10:1)	39
4	C(+)|Pt(-)	CH_3CN/MeOH (10:1)	63
5	C(+)|Pt(-)	CH_3CN	79
6	C(+)|C(-)	CH_3CN	78
7	**C(+)|Ni(-)**	**CH_3CN**	**81**
8[c]	C(+)|Ni(-)	CH_3CN	50
9[d]	C(+)|Ni(-)	CH_3CN	69
10[e]	C(+)|Ni(-)	CH_3CN	0

[a]Reaction conditions: undivided cell, **1a** (0.25 mmol), **2** (0.5 mmol), solvent (2.5 mL), $LiClO_4$ (0.2 M), CCE (15 mA), 3.2 F.mol^{-1}, rt. [b]Isolated yield. [c]*n*-Bu_4NBF_4 instead of $LiClO_4$. [d]30 mA instead of 15 Ma. [e]No current.

With the best reaction conditions in hand, we next explored the scope of the electrolytic oxytrifluoromethylation (Scheme 2). A set of representative *N*-tethered alken-6-ols with various aryl groups on the alkene proved to be suitable substrates, generating the desired morpholines in good to high yields (**3a-3f**). In general, electron-poor aromatic rings with halogen substituents reacted smoothly whereas slightly lower yield was obtained with a *para*-tert-butyl substituent. This is mainly due to a competitive trifluoromethylation of the arene ring. The *N*-2-nitrophenylsulfonyl substrates **1g** and **1h** underwent the oxytrifluoromethylation reaction with equal efficiency. Pleasingly secondary alcohol **1k** was well tolerated furnishing the corresponding 2,2,6-trisubstituted morpholine **3k** in good yield as a mixture of diastereoisomers. Moreover, enantioenriched alcohols **1i** and **1j** were successfully engaged affording the corresponding morpholines **3i** and **3j** in 36% and 65% yield, respectively, as a mixture of diastereoisomers. The lower yield with **1i** is presumably due to overoxidation of the benzylic carbon. The polycyclic compounds **3l** and **3m** were produced in descent yields albeit with moderate diastereoselectivity. To our delight, this method can also be applied to the synthesis of a difluoromethylated morpholine **3n** under slightly modified reaction conditions with 3 equivalents of CF_2HSO_2Na[18] as a source of CF_2H radical[19] in CH_3CN/H_2O (10:1). To evaluate the potential application of this protocol, a 1 mmol scale reaction of **1a** was performed under the standard reaction conditions. Delightfully, the desired morpholine product (**3a**) was obtained in a comparable yield (79%).

Scheme 2. Intramolecular Trifluoromethylation of *N*-tethered Alken-6-ols 1[a]

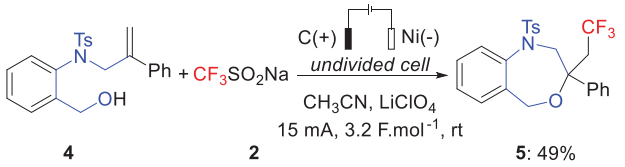


[a]Reaction conditions: undivided cell, C(+)|Ni(-), **1a** (0.25 mmol), **2** (0.5 mmol), CH_3CN (2.5 mL), $LiClO_4$ (0.2 M), CCE (15 mA), 3.2 F.mol^{-1}, rt. [b]dr were determined by ^{1}H NMR analysis of the reaction mixtures. [c]Reaction conducted on 1 mmol scale.

A further investigation revealed that the formation of seven-membered oxacycle **5** by intramolecular oxytrifluoromethylation way of *N*-tethered alken-7-ol **4** was also possible (Scheme

3). This provide a rapid access to 1,4-benzoxazepine, an important class of seven-membered rings heterocycles featuring interesting biological properties and found in numerous drugs and preclinical leads.[20]

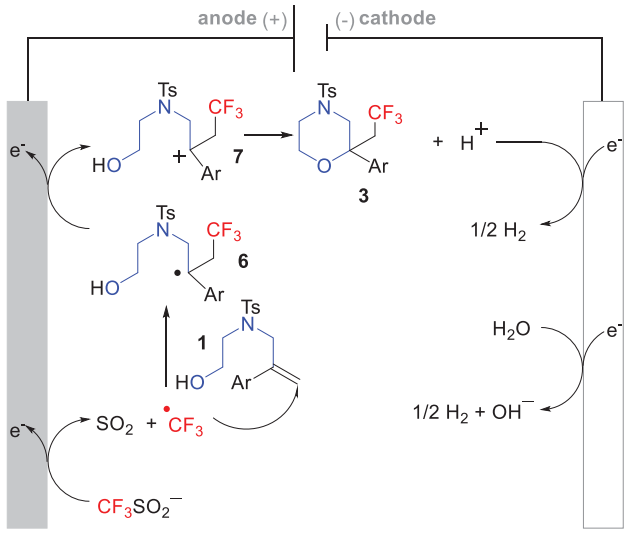
Scheme 3. Intramolecular Trifluoromethylation of *N*-tethered Alken-7-ols 4[a]



[a]Reaction conditions: undivided cell, C(+)|Ni(-), **4** (0.25 mmol), **2** (0.5 mmol), CH_3CN (2.5 mL), $LiClO_4$ (0.2 M), CCE (15 mA), 3.2 F.mol^{-1}, rt.

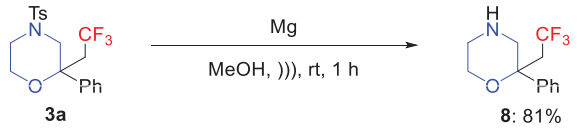
To gain more insight into the mechanism of the oxytrifluoromethylation of *N*-tethered alken-6-ols, some preliminary control experiments were performed. It is noteworthy that there is no reaction in the absence of electric current (Table 1, entry 10). Cyclic voltammetry (CV) analysis of Langlois reagent (**2**) in CH_3CN with $LiClO_4$ as electrolyte showed irreversible anodic oxidation waves (See the Supporting Information, Figure S1) at a potential much lower than that of substrate **1a** (1.48 and 2.07 V *vs* Ag/AgCl respectively). On the basis of the above results as well as other reports,[10] a plausible reaction mechanism is depicted in scheme 4. The SET anodic oxidation of CF_3SO_2Na would produce the CF_3 radical through the release of SO_2 from CF_3SO_2 radical. Subsequent regioselective addition of electrophilic CF_3 radical to alkene **1** would lead to the radical intermediate **6**, which would be further oxidized into cation **7** by a second SET anodic oxidation. Final intramolecular nucleophilic addition of the alcohol moiety would lead to the corresponding trifluoromethylated morpholine **3** along with the release of H^+. Reductions of H^+ and residual trace of water would be the counter-reactions taking place at the cathode.

Scheme 4. Plausible Mechanism



To further demonstrate the usefulness of our method to access morpholine derivatives, the tosyl group of **3a** was easily removed under mild conditions by treatment with magnesium in a sonicated methanol solution affording unprotected morpholine **8** in high yield (Scheme 5).

Scheme 5. Deprotection of Morpholine 3a



To conclude, we have developed an intramolecular radical oxytrifluoromethylation of *N*-tethered alken-6-ols by using environmentally friendly electrochemical reaction conditions with Langlois reagent as cheap and easy to handle source of trifluoromethyl radical. The procedure is suitable for the synthesis of a wide variety of functionalized oxytrifluoromethylated morpholine derivatives. This protocol was extended to a *N*-tethered alken-7-ol providing the synthesis of a CF_3-containing benzoxazepine. Extension of this method to the preparation of other trifluoromethylated heterocycles is currently underway in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/.

Experimental procedures and spectroscopic data for all compounds (PDF)

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Note

The authors declare no competing financial interest.

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