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Acid-mediated cyclizations of SEM-protected heterocyclic anilines and adjacent hydroxyls or enol-ethers

Zhaoyang Meng *, Binyuan Sun, Panduranga Adulla Reddy, M. Arshad Siddiqui †

Merck Research Laboratories, 320 Bent Street, Cambridge, MA 02141, USA

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ABSTRACT

Acid-mediated cyclizations of SEM-protected heterocyclic anilines and adjacent hydroxyls or enol ethers during SEM deprotection are reported. Strategies to suppress these side reactions and their potential synthetic utilities are also described.

[2-(Trimethylsilyl)ethoxy]methyl (SEM) has been frequently used as a protecting group for alcohols (primary, secondary, and tertiary),[1] heterocyclic NHs (indazole,[2] imidazole,[3] pyrazole,[4] indole, and pyrrole[5]), (hetero)aryl amines (primary[6] and secondary[7]), and the nitrogen of amides[8] and sulfonamides.[9] In some cases, the SEM group not only temporarily masks the reactive sites but also functions as a directing group for metalation.[5]

In general, the SEM group could be cleanly cleaved from substrates with acid or fluoride anion. However, there are several reports that when refluxing in MeOH or other alcohols in the presence of catalytic amounts of HCl, some SEM-protected compounds could be transformed to the corresponding MOM-protected derivatives or related alkoxyaminals based on the alcohols used.[10] In our research, we observed that some SEM-protected heterocyclic anilines might involve in ring formation side reactions with adjacent functional groups, such as hydroxyls or enol-ethers, during the acidic deprotection process. Herein, we report this interesting reactivity of the SEM group. Strategies to suppress these side reactions and their potential synthetic utilities are also described.

During the course of a medicinal chemistry program, we planned to prepare compound **5** for testing and the initial synthetic route is outlined in Scheme 1. After aldehyde **1** was reduced by $NaBH_4$ to the corresponding primary alcohol **2**, the desired alcohol **5** was not observed when **2** was treated with 50% TFA/H_2O to remove the 8-amino's bis-SEM protecting groups.[11] Instead, **2** was cleanly converted to an unexpected major product **3** which showed a molecular ion peak at *m*/*z* 436 $(M+H)^+$, 12 higher than the calculated value of **5**.[12] This suggested that compared to **5**, **3** has an extra carbon atom present in the molecule. We proposed that this specific carbon atom was from one of the SEM protecting groups and **3** had the 2,4-dihydro-1*H*-pyrazolo[5′,1′:2,3]pyrimido[4,5-*d*][1,3]oxazine core structure. Indeed, the ^1H NMR spectra exhibits characteristic features of this structure: singlet at 5.01 ppm and doublet at 5.03 ppm corresponding to the two CH_2 groups of the dihydrooxazine ring. The tricyclic structure assignment was further confirmed through detailed 2D NMR studies (Fig. 1).

The originally targeted **5** was eventually made by reversing the reaction sequence, with the SEM deprotection performed prior to the aldehyde reduction as shown in Scheme 1.[13]

A similar ring closure reaction was observed when the diol analog **6** was treated with HCl to provide **7** as shown in Scheme 2.[11]

As part of the same drug discovery program, we also targeted ketone **9**, which we planned to prepare from the SEM-protected enol ether **8** by acid treatment as demonstrated in Scheme 3. Interestingly, we found that the product of this step was highly dependant on the acid used.[13,14] Ketone **9** was obtained as expected when using 50% TFA/H_2O as the acid; however, the unexpected **10** was isolated when switching to a non-aqueous acid, such as

* Corresponding author at present address: Merck Research Laboratories, 770 Sumneytown Pike, PO Box 4, West Point, PA 19486, USA. Tel.: +1 215 652 6199.
E-mail address: zhaoyang.meng@merck.com (Z. Meng).
† Present address: Paraza Pharma Inc., 500 Boulevard Cartier (West), Laval, Quebec H7V 5B7, Canada.

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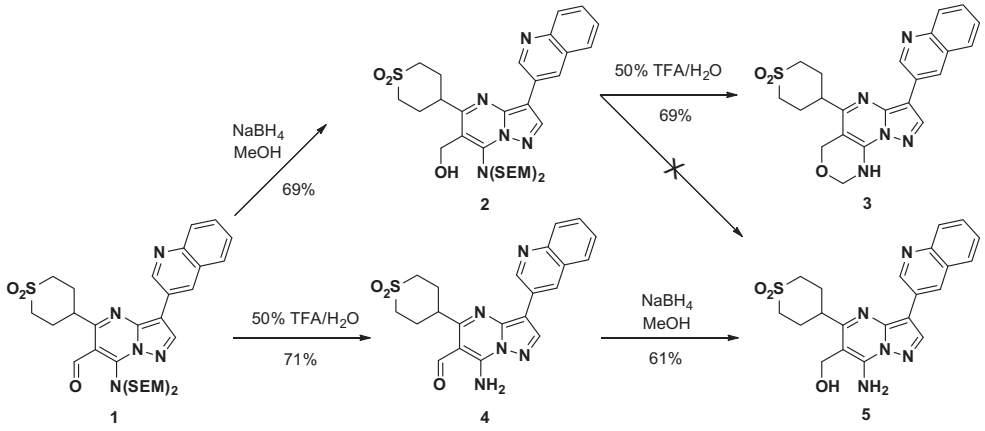


Scheme 1. Preparation of **3** and **5**.

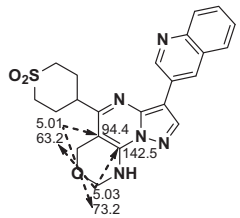
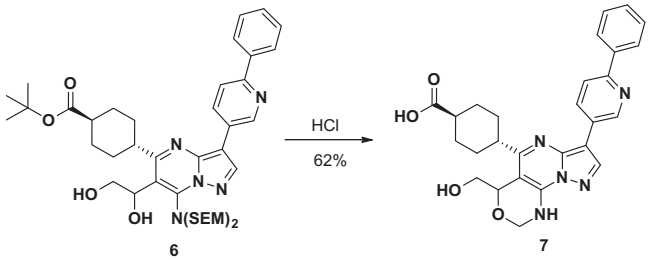


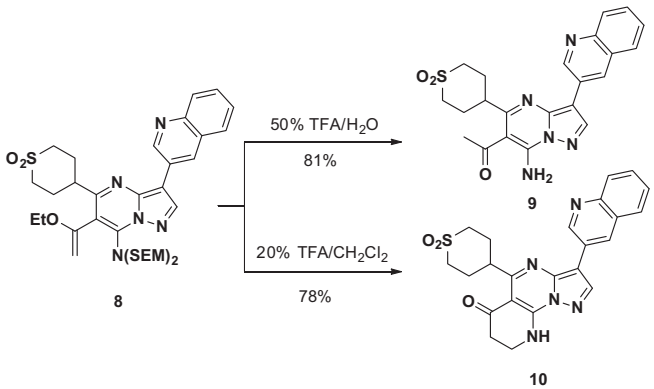
Figure 1. Selected ^{1}H and ^{13}C chemical shifts and HMB correlation of **3**.

neat TFA or 20% TFA/CH_2Cl_2.[15] Similar to the previous case shown in Scheme 1, the molecular weight difference between **9** and **10** was 12. We suspected that a piperidin-4-one ring was formed involving the bis-SEM protecting groups and the adjacent enol ether group. The tricyclic core structure of **10**, 8,9-dihydropyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-6(7*H*)-one, was confirmed by extended 2D NMR studies (Fig. 2).

A plausible mechanism of these SEM group involved cyclization reactions is described in Scheme 4. Upon acid treatment, SEM-protected heterocyclic anilines **2** and **8** are converted to hemaminals **3′** and **10′**, respectively, which could be further transformed to the corresponding iminium intermediate **3″** and **10″**. Both



Scheme 2. Preparation of **7**.



Scheme 3. Preparation of **9** and **10**.

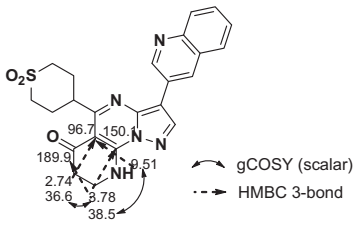


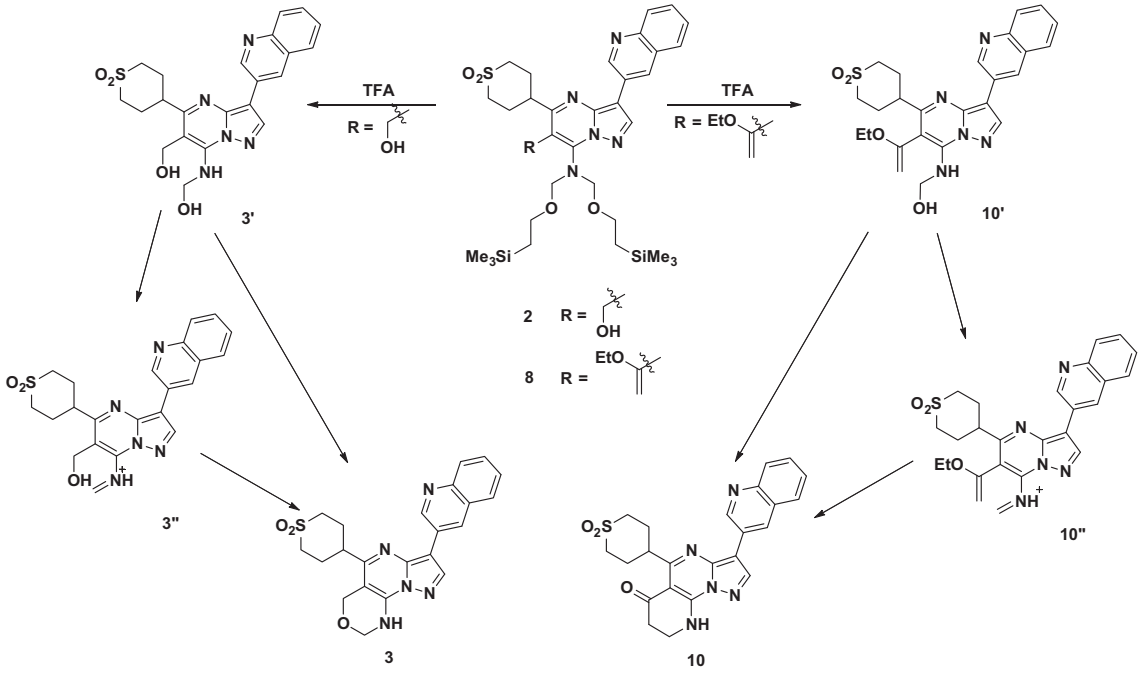
Figure 2. Selected ^{1}H and ^{13}C chemical shifts and *g*COSY/HMBC correlation of **10**.

hemiaminals **3′** and **10′** react consecutively with the neighboring hydroxy or enol ether via proton catalysis to afford the two tricyclic analogs, **3** and **10**, respectively in high yield. Alternatively, **3** and **10** could also be considered as generated by an intramolecular addition of the adjacent hydroxy or enol ether to the iminium double bond in intermediate **3″** and **10″**.

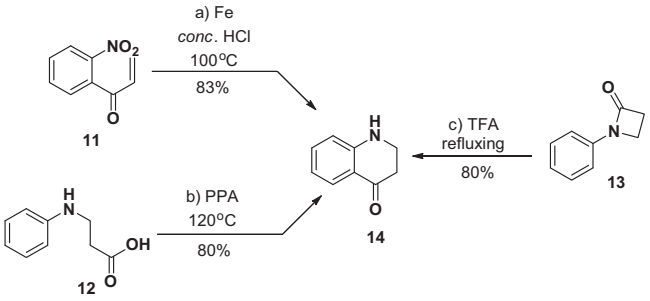
Piperidin-4-one and its related analogs are common features in a number of natural products[16] and versatile intermediates in the preparation of a range of pharmaceutical active agents.[17] As shown in Scheme 5, their general synthetic routes include: (a) reductive cyclization of 1-(2-nitro-phenyl)-2-propen-1-one **11** using iron powder in concentrated HCl;[18] (b) Friedel–Crafts cyclization of 3-(phenylamino)propanoic acid **12** in hot polyphosphoric acid (PPA) or hot methanesulfonic acid;[19] (c) acid catalyzed Fries rearrangement of 1-arylazetidin-2-one **13**.[20]

We considered that the ring formation strategy involving the SEM group and a neighboring enol ether group had the potential to be an alternative method of preparing important piperidin-4-ones and related structures. As listed in Table 1, a series of substrates with different substituents were submitted to TFA treatment. To our delight, all reactions provided the tricyclic systems in moderate to high yield.[14]

In summary, we have identified unknown cyclizations between SEM-protected heterocyclic anilines and adjacent hydroxyls or enol-ethers. While these side reactions could be limited through altering the reaction sequence or reaction conditions, these ring formation strategies have proved to be synthetically useful as demonstrated by a variety of examples with different substituents. Further developments in this area will be reported in due course.

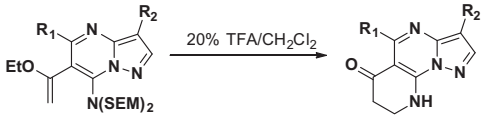


Scheme 4. Proposed mechanism.

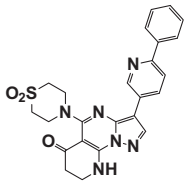
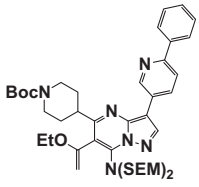
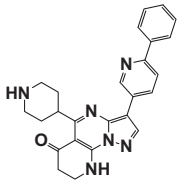
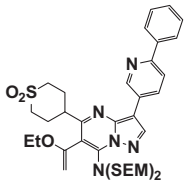
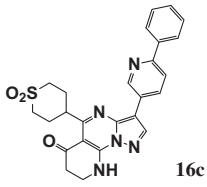
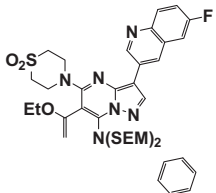
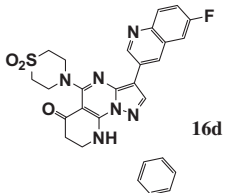
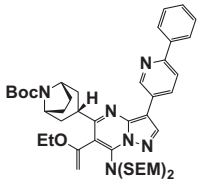
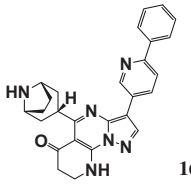
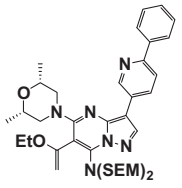
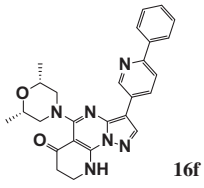
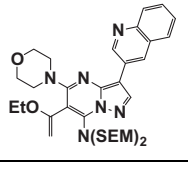
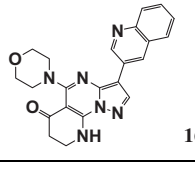


Scheme 5. Known synthetic routes of piperidin-4-one and analogs.

Table 1
Acid-mediated cyclization of SEM-protected heterocyclic anilines and enol-ethers



15 16

Entry	SEM protected substrates **15**	Products **16**	Yield (%)
1	 **15a**	 **16a**	72
2	 **15b**	 **16b**	85
3	 **15c**	 **16c**	75
4	 **15d**	 **16d**	99
5	 **15e**	 **16e**	80
6	 **15f**	 **16f**	84
7	 **15g**	 **16g**	68

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12. *Representative procedure for the synthesis of dihydrooxazine derivatives*: preparation of 4-(7-(quinolin-3-yl)-2,4-dihydro-1*H*-pyrazolo[5′,1′:2,3]pyrimido[4,5-*d*][1,3]oxazin-5-yl)tetrahydro-2*H*-thiopyran 1,1-dioxide (**3**). At 0 °C, **2** (21 mg, 0.031 mmol) was treated with 50% TFA/H_2O (1 mL). The mixture was slowly warmed up to room temperature and stirred at the same temperature overnight. Concentration and purification by RP-HPLC (20–80% CH_3CN/H_2O with 0.1% TFA) provided **3** (11.7 mg, 69%). ^{1}H NMR (DMSO-d_6) δ: (ppm)) 9.86 (d, 1H, J = 2.12 Hz), 9.16 (s, 1H), 9.05 (s, 1H), 8.90 (s, 1H), 8.04 (d, 1H, J = 8.43 Hz), 7.97 (d, 1H, J = 8.14 Hz), 7.77 (t, 1H, J = 7.65 Hz), 7.69 (t, 1H, J = 7.53 Hz), 5.03 (d, 2H, J = 3.10 Hz), 5.01 (s, 2H), 3.38 (dd, 2H, J = 13.64, 2.99 Hz), 3.27 (d, 2H, J = 13.64 Hz), 3.14 (tt, 1H, J = 11.31, 3.00 Hz), 2.42 (dt, 2H, J = 12.41, 2.11 Hz), 2.21 (d, 2H, J = 12.79 Hz). ^{13}C NMR (DMSO-d_6) δ: (ppm) 159.3, 146.1, 144.4, 142.7, 142.5, 142.4, 130.8, 129.4, 128.1, 127.7, 127.7, 126.8, 126.5, 103.0, 94.4, 73.2, 63.2, 50.0, 36.9, 28.8. HRMS calcd for [M+H]: 436.1418. Found: 436.1438.
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15. *Representative procedure for the synthesis of piperidin-4-one derivatives*: preparation of 5-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-3-(quinolin-3-yl)-8,9-dihydropyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-6(7*H*)-one (**10**). At 0 °C, TFA (1 mL) was added in one portion to **8** (36.9 mg, 0.051 mmol). The mixture was slowly warmed up to room temperature and stirred at the same temperature for 1 h. Concentration and purification by RP-HPLC (20–80% CH_3CN/H_2O with 0.1% TFA) provided **10** (22.2 mg, 78%). ^{1}H NMR (DMSO-d_6) δ: (ppm)) 9.82 (d, 1H, J = 2.16 Hz), 9.51 (s, 1H), 9.09 (s, 1H), 9.03 (s, 1H), 8.05 (d, 1H, J = 8.37 Hz), 7.99 (d, 1H, J = 8.15 Hz), 7.79 (t, 1H, J = 7.63 Hz), 7.69 (t, 1H, J = 7.51 Hz), 4.18 (tt, 1H, J = 10.52, 3.62 Hz), 3.78 (ddd, 2H, J = 7.44, 2.60 Hz), 3.34 (ddd, 2H, J = 14.16, 43.58 Hz), 3.26 (dd, 2H, 14.16, 3.54 Hz), 2.74 (t, 2H, J = 7.29 Hz), 2.35 (dt, 2H, J = 12.27), 2.28 (br obs, 2H). ^{13}C NMR (DMSO-d_6) δ: (ppm) 189.9, 164.1, 150.1, 147.8, 144.2, 144.0, 143.7, 131.5, 129.5, 128.0, 128.0, 127.7, 127.6, 125.8, 106.2, 96.7, 50.5, 39.4, 38.5, 36.6, 28.9. HRMS calcd for [M+H]: 448.1418. Found: 448.1438.
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