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# Facile synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepin-3-ones *via* cyclization of *N*-alkoxy α-halogenoacetamides with *N*-(2-chloromethyl)aryl amides†

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**A facile and efficient cyclization of *N*-alkoxy α-halogenoacetamides with *N*-(2-chloromethyl)aryl amides has been achieved for rapid access to 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one derivatives (up to 95% yield). The intriguing features of this intermolecular cyclization include its mild reaction conditions and easy handling for scalable synthesis.**

Benzodiazepines, a member of the family of core structural subunits, occupy a significant place among pharmaceutical ingredients.[1] These compounds have been extensively studied for their manifold bioactivities. Some representative examples are shown in Fig. 1: diazepam is used to treat anxiety;[1a] abbemycin, isolated from *Streptomyces* sp. AB-999F-52, is an antibiotic.[2] Although 1,4-benzodiazepine-2-ones have been widely studied, their analogues 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones have been less investigated. They have recently attracted considerable attention due to their highly diverse activities, such as being a potent inhibitor of the vitamin D receptor in Paget's disease of bone,[3] PARP inhibitor[4] and protein kinase C modulator[5] for anticancer drugs.

Consequently, during the past decades, various synthetically feasible protocols have been developed to construct this coveted moiety through intramolecular cyclization pathways. The existing methods for the synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones typically are intramolecular nucleophilic aromatic substitution,[6] intramolecular cycloaddition,[7] palladium-catalyzed *N*-arylation[8] and Ullmann's aryl amination (Scheme 1a).[9] Although these methods provide convenient access to 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one derivatives, the reported applications suffer from drawbacks such as multistep reactions and harsh reaction conditions (transition metal catalyzed cyclization and/or high temperature). In light of the above-mentioned limitations, the explora-

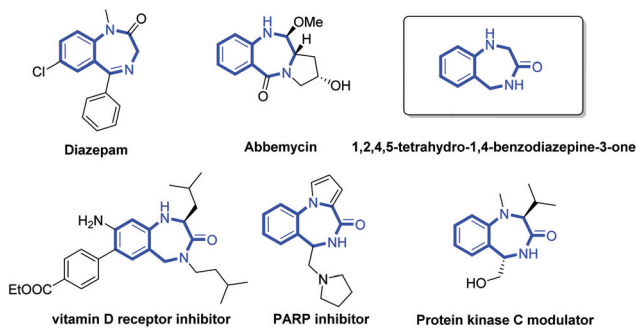
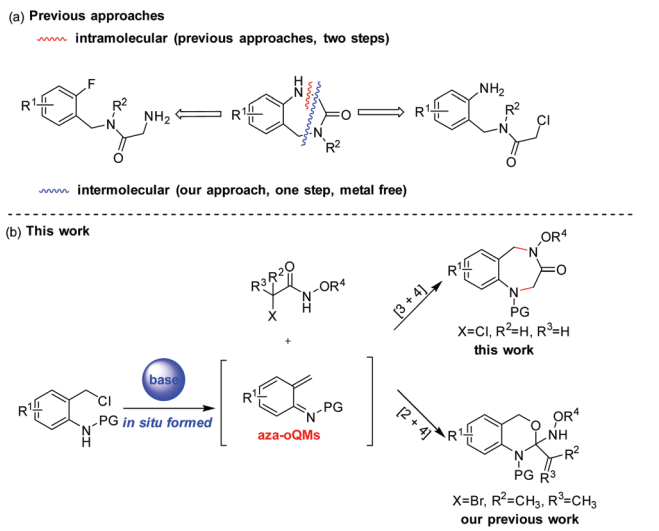



**Fig. 1** Representative biologically active compounds containing the benzodiazepine skeleton.




**Scheme 1** Previous reports on and our approach for the synthesis of 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones.

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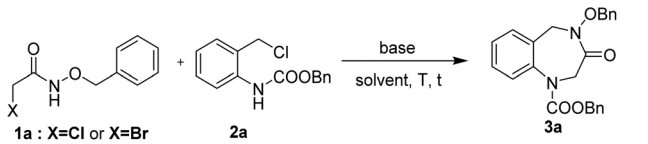
tion of newer and sustainable methods under benign conditions to access diverse 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones is still in high demand.

In recent years, azaoxyallyl cations, generated *in situ* from *N*-alkoxy α-halogenoacetamides in the presence of a base, constitute a class of versatile building blocks useful for the rapid construction of biologically important molecules. In their pioneering work, Jeffrey's group reported inter- and intramolecular [4 + 3] cycloadditions of azaoxyallyl cations with furans for heterocycle synthesis.[10] After that, azaoxyallyl cations, such as 1,3-dipoles, have been widely applied in [3 + 1]-,[11] [3 + 2]-,[12] and [3 + 3]-[13] cycloaddition reactions. Recent investigations also revealed that aza-*o*-quinone methides (aza-oQMs), generated *in situ* through the base-mediated elimination of *N*-(2-chloromethyl)aryl amides, have been widely used as the new reactive synthons in [4 + m] cycloaddition reactions.[14] Because of their high reactivity profiles, we firstly envisioned a direct pathway to assemble 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones *via* [3 + 4] annulation of *N*-alkoxy α-halogenoacetamides with aza-oQMs (Scheme 1b). Unexpectedly, a cyclization reaction proceeded *via* [2 + 4] annulation when we started to investigate the model reaction of 3-(((2-bromo-2-methylpropanamido)oxy)methyl)benzene-1-ylium with methyl(2-(chloromethyl)phenyl)carbamate (Scheme 1b).[15] Inspired by this result, we observed that the [2 + 4] annulation of dialkyl substituted haloamides proceeded efficiently with aza-oQMs. As part of our efforts in developing the [3 + 4] annulation of *N*-alkoxy α-halogenoacetamides with aza-oQMs, we describe here our work on the aforementioned reaction of unsubstituted haloamides with aza-oQMs.

Our work commenced with the screening of various parameters in order to search for the ideal reaction conditions for an efficient and successful annulation of *N*-OBn substituted chloroacetamide derivative **1a** with benzyl (2-(chloromethyl) phenyl)carbamate **2a** (Table 1). Initially, it was found that $Cs_2CO_3$ (2.0 equiv.) was effective in promoting this transformation, affording our desired [3 + 4] product in 58% yield in DMF at room temperature in 4 h (entry 1, Table 1). Then, systematic optimization of the reaction conditions was performed. A series of bases were explored. Inorganic bases, such as *t*-BuOK, NaOH and KOH, failed to produce the expected product (entries 4–6, Table 1), and the other bases such as $K_2CO_3$, $Na_2CO_3$ and NaOMe exhibited comparable activity (entries 2, 3 and 7, Table 1). As is shown, among the several commonly used inorganic bases, $Cs_2CO_3$ was proven to be the most effective choice. Organic bases such as $Et_3N$, DIPEA, DMAP and DBU were found to be ineffective for this reaction (entries 8–11, Table 1). Next, the amount of $Cs_2CO_3$ was varied (entries 12 and 13, Table 1). By performing the reaction with $Cs_2CO_3$ (2.5 equiv.), the reaction proceeded smoothly and the yield of **3a** increased to 75% (entry 12, Table 1). Further, the effect of solvent was examined (entries 14–21, Table 1). A survey was conducted on alternative solvents such as 1,4-dioxane, toluene, THF, DCM, DCE, $CH_3CN$, HFIP and DMAc, which revealed that DMF was the optimal solvent of choice. Finally, temperature has a little effect on the reaction. High temperature resulted in slightly decreased yields (entry 23, Table 1). An *N*-OBn substituted bromoacetamide derivative was also used for the preparation of **3a** during the exploration of the reaction scope (entry 22, Table 1).

**Table 1** Optimization of the reaction conditions[a]

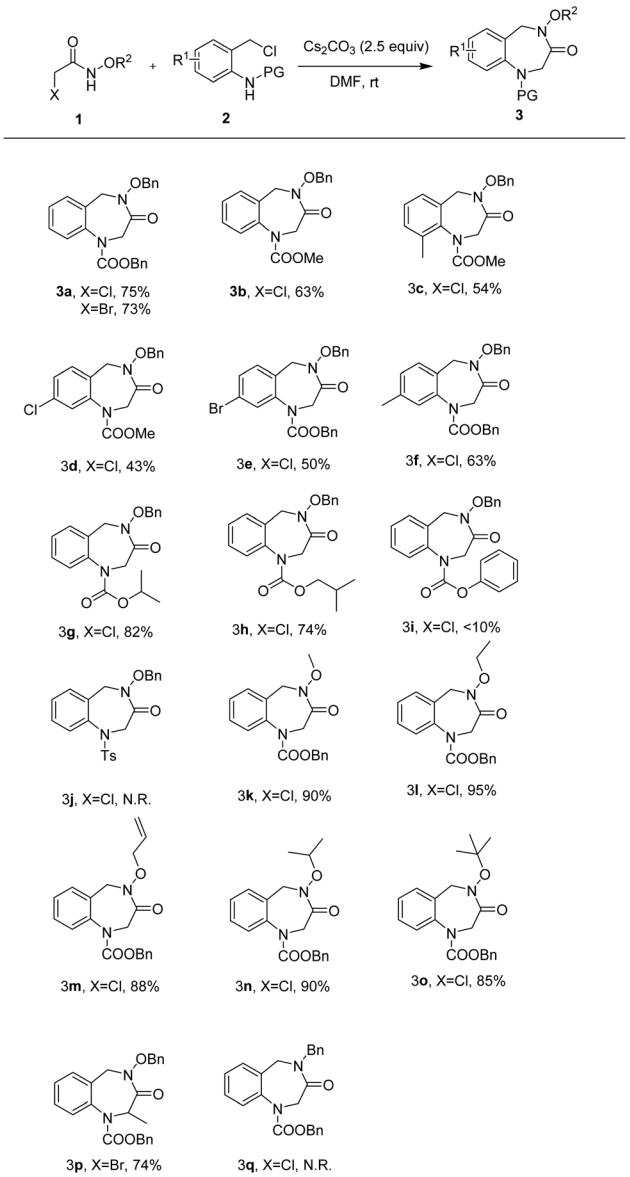



1a : X=Cl or X=Br 2a 3a

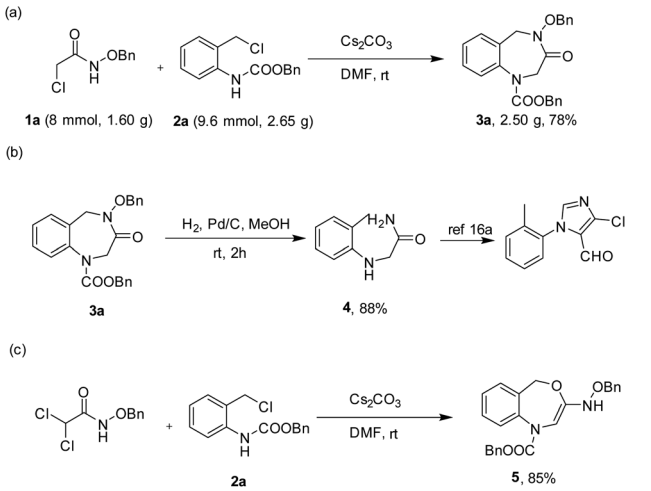
| Entry | Base (equiv.) | X | Solvent | Temp. (°C) | Time (h) | Yield of **3a**[b] (%) |
|---|---|---|---|---|---|---|
| 1 | $Cs_2CO_3$ (2.0) | Cl | DMF | rt | 4 | 58 |
| 2 | $K_2CO_3$ (2.0) | Cl | DMF | rt | 4 | 47 |
| 3 | $Na_2CO_3$ (2.0) | Cl | DMF | rt | 4 | 42 |
| 4 | *t*-BuOK (2.0) | Cl | DMF | rt | 4 | <10 |
| 5 | NaOH (2.0) | Cl | DMF | rt | 4 | — |
| 6 | KOH (2.0) | Cl | DMF | rt | 4 | Trace |
| 7 | NaOMe (2.0) | Cl | DMF | rt | 4 | 27 |
| 8 | $NEt_3$ (2.0) | Cl | DMF | rt | 4 | — |
| 9 | DIPEA (2.0) | Cl | DMF | rt | 4 | — |
| 10 | DMAP (2.0) | Cl | DMF | rt | 4 | — |
| 11 | DBU (2.0) | Cl | DMF | rt | 4 | 17 |
| **12** | **$Cs_2CO_3$ (2.5)** | **Cl** | **DMF** | **rt** | **3** | **75** |
| 13 | $Cs_2CO_3$ (3.0) | Cl | DMF | rt | 3 | 73 |
| 14 | $Cs_2CO_3$ (2.5) | Cl | 1,4-Dioxane | rt | 3 | 43 |
| 15 | $Cs_2CO_3$ (2.5) | Cl | Toluene | rt | 3 | 35 |
| 16 | $Cs_2CO_3$ (2.5) | Cl | THF | rt | 3 | 55 |
| 17 | $Cs_2CO_3$ (2.5) | Cl | DCM | rt | 3 | 37 |
| 18 | $Cs_2CO_3$ (2.5) | Cl | DCE | rt | 3 | 45 |
| 19 | $Cs_2CO_3$ (2.5) | Cl | $CH_3CN$ | rt | 3 | 65 |
| 20 | $Cs_2CO_3$ (2.5) | Cl | HFIP | rt | 3 | Trace |
| 21 | $Cs_2CO_3$ (2.5) | Cl | DMAc | rt | 3 | 62 |
| 22 | $Cs_2CO_3$ (2.5) | Br | DMF | rt | 3 | 73 |
| 23 | $Cs_2CO_3$ (2.5) | Cl | DMF | 45 | 3 | 68 |

[a] Unless noted otherwise, reaction of **1a** (0.2 mmol), **2a** (0.24 mmol) and base was performed in 2.0 mL of solvent under Ar. [b] Isolated yield based on **1a**.

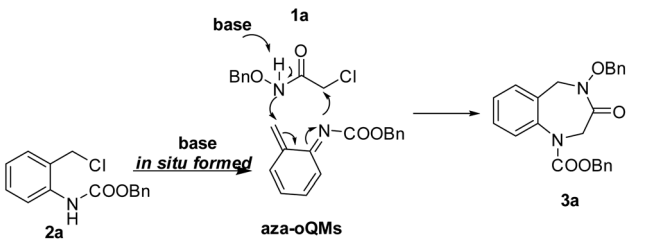
Having identified the optimal reaction parameters, we then focused on the exploration of the reaction scope (Scheme 2). Initially, a variety of *N*-(*ortho*-chloromethyl)aryl amides **2** were examined. *N*-(*ortho*-Chloromethyl)aryl amides **2** with electron-withdrawing or electron-donating groups at different positions were well tolerated in this reaction (**3c**: 54%, **3d**: 43%, **3e**: 50%, and **3f**: 63%). In addition, the reaction of the *N*-protecting group of **2** either resulted in moderate yields or did not work at all. The *N*-Cbz group, *N*-COOMe group, *N*-COOi-Pr group and *N*-COOi-Bu group afforded the corresponding products in moderate yields. Nevertheless, the *N*-Ts group was not suitable and the expected product was not formed. Finally, we moved toward investigating the reactivity of the *N*-alkoxy α-halogenoacetamide partner. As expected, the reactions of these unsubstituted *N*-alkoxy α-halogenoacetamides worked equally smoothly to give the desired products in good yields. Hydroxamates with variation in their protecting groups on the nitrogen atom such as methoxy, ethoxy, allyloxy, isopropoxy and *tert*-butoxy tend to provide 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-one derivatives in 85–95% yields (**3k–3o**). The reaction was also efficient when *N*-(benzyloxy)-2-bromopropana-




**Scheme 2** The reaction scope. Typical conditions: $Cs_2CO_3$ (2.5 equiv.) was added to a stirred solution of **1** (0.2 mmol) and **2** (0.24 mmol) in DMF (2.0 mL) at room temperature for 3 h under an Ar atmosphere. Isolated yield based on **1**.




**Scheme 3** Follow-up chemistry.




**Scheme 4** Plausible reaction mechanism.

mide was used, leading to the desired product **3p** in 74% yield. However, *N*-benzyl-2-chloroacetamide was found to be not suitable for this reaction, and no desired product was observed.

In order to address the viability and potential synthetic application of this reaction, gram-scale scale-up reactions and several applications were carried out (Scheme 3). Product **3a** was obtained in a sustained yield (78%) on an 8 mmol scale under the standard conditions (Scheme 3a). Next, the deprotection of the benzyloxy group of **3a** was performed. We found that both the C–N bond and the benzyloxy group of **3a** were readily transformed through hydrogenation with Pd/C in methanol solvent. The glycinamide product **4** is an important intermediate that was used to afford 1-alkyl(aryl)-4-chloro-1*H*-imidazole-5-carbaldehydes (Scheme 3b).[16a] To further investigate the reaction scope, *N*-(benzyloxy)-2,2-dichloroacetamide was tested. Curiously, the unexpected product **5** was obtained in 85% yield (Scheme 3c).

On the basis of our results and the previous studies,[17] a plausible mechanism was proposed as illustrated in Scheme 4. First, *N*-(*ortho*-chloromethyl)aryl amide **2a** reacts with $Cs_2CO_3$ to form the *in situ* generated aza-oQM intermediates. Then, deprotonation on the nitrogen atom of *N*-alkoxy α-halogenoacetamide **1a** occurred under the promotion of a base. Finally, the reaction might occur through a cascade aza-Mannich addition/intramolecular $S_N2$ pathway to generate the final domino product **3a**.

In summary, *N*-alkoxy α-halogenoacetamides and aza-oQMs formed *in situ* undergo a cascade aza-Mannich addition/intramolecular $S_N2$ domino reaction to provide synthetically useful 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones in average to good yields (up to 95% yield). The present methodology is a concise, mild, practical and one-pot method. Further studies on the application of 1,2,4,5-tetrahydro-1,4-benzodiazepine-3-ones are underway in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

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