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I_2-Promoted Multicomponent Dicyclization and Ring-Opening Sequences: Direct Synthesis of Benzo[*e*][1,4]diazepin-3-ones via Dual C−O Bond Cleavage

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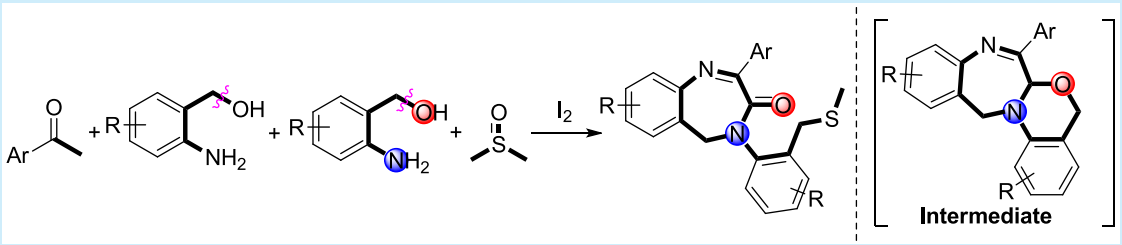
Supporting Information



ABSTRACT: A novel and efficient formal [4 + 2+1] annulation of aryl methyl ketones and 2-aminobenzyl alcohols for the synthesis of benzo[*e*][1,4]diazepin-3-ones is reported. This reaction successfully affords diverse seven-membered ring lactams via dual C−O bond cleavage. A preliminary mechanistic study showed that a multicomponent dicyclization and ring-opening sequence might occur, with the introduction of methyl sulfide proposed as the last step. This efficient strategy with mild reaction conditions and a broad substrate scope has potential applications in chemistry and medicine.

The 1,4-benzodiazepine skeleton, first discovered in the 1960s,[1] exhibits an indispensible role in the field of pharmaceutical chemistry owing to its biological activity.[2] In the last several decades, the variety of 1,4-aryldiazepine-containing compounds has been greatly enriched, with some shown to be effective as pharmaceutical drugs.[3] Notably, several marketed drugs feature 1,4-benzodiazepine cores, including diazepam[4] (among the most successful drugs for treating a wide spectrum of central nervous system disorders), bretazenil[5] (a partial agonist for GABAA receptors), flumazenil[6] (a high-affinity GABAA-BZ site antagonist), and devazepide[7] (a cholecystokinin (CCK) antagonist). Owing to their medicinal value, further developing direct strategies for the synthesis of novel 1,4-benzodiazepine-containing compounds, particularly efficient and practical multicomponent cyclization, is highly valuable and urgent.

The construction of N-containing fused heterocycles by direct annulation of *o*-substituted aniline derivatives is a fascinating topic[8] owing to their high reactivity and easy availability. Among these substrates, 2-aminobenzyl alcohols are among the most popular reagents for the construction of *N*-heterocyclic compounds owing to their versatile reactivity. According to numerous documented works,[9] 2-aminobenzyl alcohols are usually used as four-atom or five-atom components to construct *N*,*O*/*N*-containing heterocyclic compounds via formal [5 + 1], [4 + 1], or [4 + 2] cycloadditions. However, most of these studies have focused on two-component reactions, which limit the complexity of products and novelty of reactions to some extent. Although significant progress has been achieved in multicomponent reactions involving 2-aminobenzyl alcohols, they remain rare.[10−12] For example, the Wu group[10] presented a novel copper-catalyzed three-components reaction for the synthesis of diverse 2-substituted quinazolines via formal [4 + 2] annulation (Scheme 1a). Furthermore, several multicomponent cascade cyclizations have been achieved. Recently, Yu[11] and co-workers reported an acid-promoted three-component cascade reaction of glyoxal monohydrates, amine alcohols, and KSCN to construct a wide range of bicyclization products under mild conditions. Notably, this efficient strategy was green, with a short reaction time followed by a group-assisted purification (GAP) chemistry process (Scheme 1b). Later, our group[12] described a novel four-component tandem cyclization process to construct fused heterocycles from commercially available glyoxal monohydrates and 2-aminobenzyl alcohols. Unfortunately, only the major stereoisomers were isolated in moderate yields (Scheme 1c). Although these reports are elegant and important, they have focused on the construction of six-membered rings. Using 2-aminobenzyl alcohols to access medium-sized rings via multicomponent reactions is an underdeveloped approach. Therefore, further exploring the reactivity of 2-aminobenzyl alcohols for the construction of medium-sized rings remains a valuable and challenging research area. In continuation of the hot research topic in building diverse heterocycles,[13] we herein disclose an iodine-

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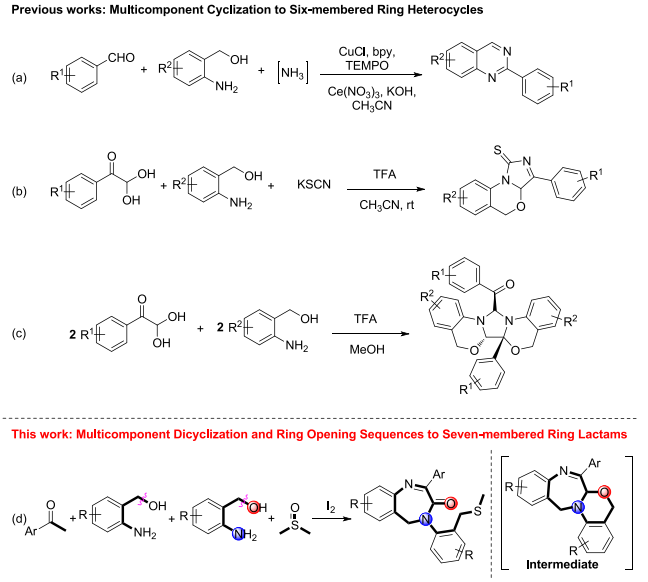
Scheme 1. Multicomponent Reactions Involving 2-Aminobenzyl Alcohols

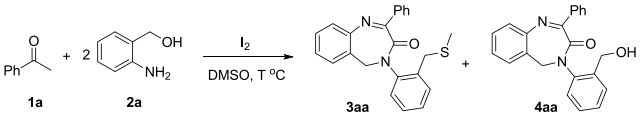


promoted multicomponent dicyclization and ring-opening sequence of aryl methyl ketones, 2-aminobenzyl alcohol, and *in situ* generated dimethyl sulfide (DMS) for the construction of a variety of novel benzo[*e*][1,4]diazepin-3-ones, which have not been reported in previous works (Scheme 1d).

The study was initiated using acetophenone (**1a**) and 2-aminobenzyl alcohol (**2a**) as model substrates. Fortuitously, **1a** and **2a** underwent multicomponent reactions, affording products **3aa** (X-ray of **3aa** in the SI) and **4aa** in 52% and 17% yields, respectively (Table 1, entry 1). We next tested various conditions to improve the yield of **3aa**. First, different temperatures were examined, with 100 °C found to be the optimal temperature (Table 1, entries 1−4). Further screening of different amounts of iodine showed that 1.6 equiv was the best choice (Table 1, entries 5−8). To further improve the yield of **3aa**, diverse additives were evaluated, including TFA, HI, $FeCl_3$, $Cu(OAc)_2$, oxone, and T_3P, but gave inferior yields (Table 1, entries 9−14). We speculated that the low concentration of *in situ* generated DMS was a main factor in the unsatisfactory yields of **3aa**. Therefore, we examined the effect of the amount of DMS on the reaction. When 4.0 equiv of DMS (liquid, >99%) was added, **3aa** was obtained in 73% yield with trace amounts of **4aa**. However, the yield of **3aa** showed no significant increase when the amount of DMS was further increased to 6.0 equiv (Table 1, entries 15−17).

With optimal conditions in hand, we examined the scope of aryl and heteroaryl methyl ketone substrates in this four-component reaction. Diversely substituted methyl ketones underwent formal [4 + 2 + 1] annulations to furnish the desired seven-membered ring products in moderate to good yields. As shown in Scheme 2, aryl methyl ketone substrates bearing electron-rich groups afforded the cyclization products in good yields (66%−75%, **3aa**−**3ga**). Aryl methyl ketones bearing halogen functional groups (4-F, 4-Cl, 4-Br, and 3,4-di-Cl) gave the desired compounds in satisfactory yields (68%−76%, **3ha**−**3ka**). Furthermore, electron-deficient substrates bearing phenyl, methylsulfonyl, or cyano groups at the *para*-position or a nitryl group at the *meta*-position reacted smoothly to give the desired products in moderate yields

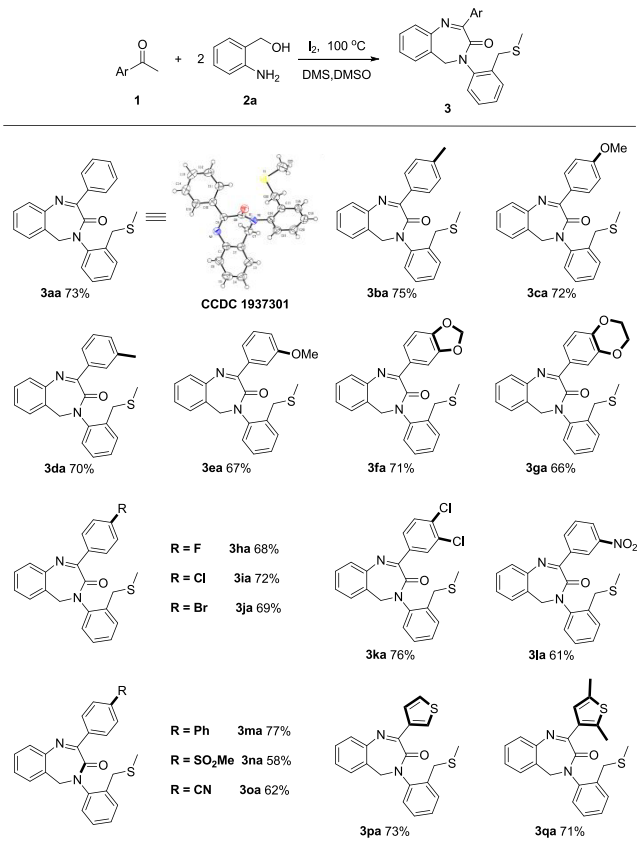
Table 1. Representative Optimization Conditions[a]



entry	I_2 (equiv)	temp (°C)	additive	yield of **3aa** (%)[b]	yield of **4aa** (%)[b]
1	1.6	90		52	17
2	1.6	100		56	19
3	1.6	110		48	18
4	1.6	120		43	15
5	0.4	100		0	trace
6	1.0	100		50	20
7	2.0	100		17	23
8	3.0	100		trace	16
9	1.6	100	TFA	47	22
10	1.6	100	HI	49	23
11	1.6	100	$FeCl_3$	trace	18
12	1.6	100	$Cu(OAc)_2$	trace	25
13	1.6	100	oxone	trace	21
14	1.6	100	T_3P[f]	0	0
15[c]	1.6	100	DMS	66	8
16[d]	**1.6**	**100**	**DMS**	**73**	**trace**
17[e]	1.6	100	DMS	74	trace

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), I_2 (*x* mmol), additive (0.5 mmol, 1.0 equiv), indicated temperature, DMSO 3 mL, unless otherwise noted. [b]Isolated yields. [c]DMS (2.0 equiv, liquid, >99%). [d]DMS (4.0 equiv, liquid, >99%). [e]DMS (6.0 equiv, liquid, >99%). [f]T_3P (propylphosphonic acid anhydride).

Scheme 2. Scope of Aryl Methyl Ketones[a,b]



[a]0.5 mmol scale. [b]Isolated yield of products **3**.

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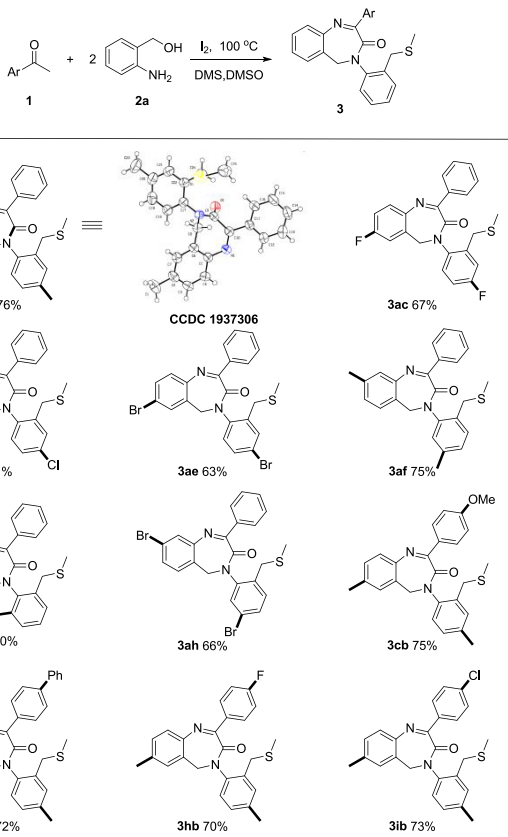
(58%–77%, **3la**–**3oa**). Pleasingly, when 3-acetylthiophene **1p** and 1-(2,5-dimethylthiophen-3-yl)ethanone **1q** were used as substrates, desired products **3pa** and **3qa** were obtained in 73% and 71% yields, respectively.

To further examine the generality of this four-component reaction, a brief screening of other commercially available 2-aminobenzyl alcohols was conducted (Scheme 3). For

Scheme 3. Scope of 2-Aminobenzyl Alcohols[a,b]



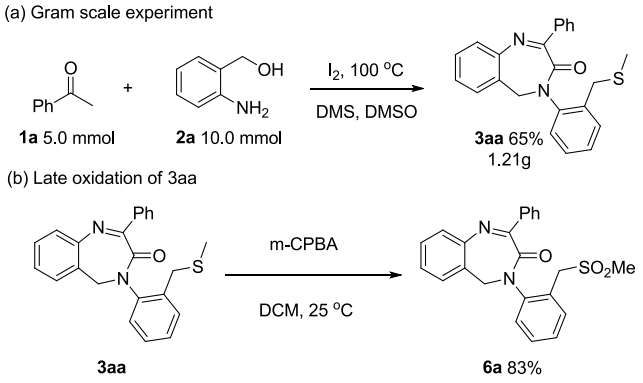
[a]0.5 mmol scale. [b]Isolated yield of products **3**.

example, substrates with methyl and halogen groups (F, Cl, and Br) at the 5-position were compatible, affording the corresponding products in moderate isolated yields (63%–76%, **3ab**–**3ae**). Substrates with methyl groups at the 4- or 3-positions were also well tolerated, affording **3af** and **3ag** in 75% and 70% yields, respectively. Substrates with Br at the 4-position were also tolerated (66%, **3ah**). Furthermore, 5-methyl-2-aminobenzyl alcohol reacted smoothly with aryl methyl ketones bearing methoxy, fluorine, chlorine, and phenyl groups at the *para*-position to give the corresponding products in good to moderate yields (70%–75%; **3cb**, **3mb**, **3hb**, and **3ib**).

To demonstrate the synthetic potential of this method, a gram-scale reaction was conducted under standard conditions, affording **3aa** in 65% yield. With **3aa** in hand, late-stage oxidation was briefly implemented by treating **3aa** with *m*-CPBA (1.5 equiv) in DCM at 25 °C to give sulfone-containing product **6a** in 83% yield (Scheme 4b).

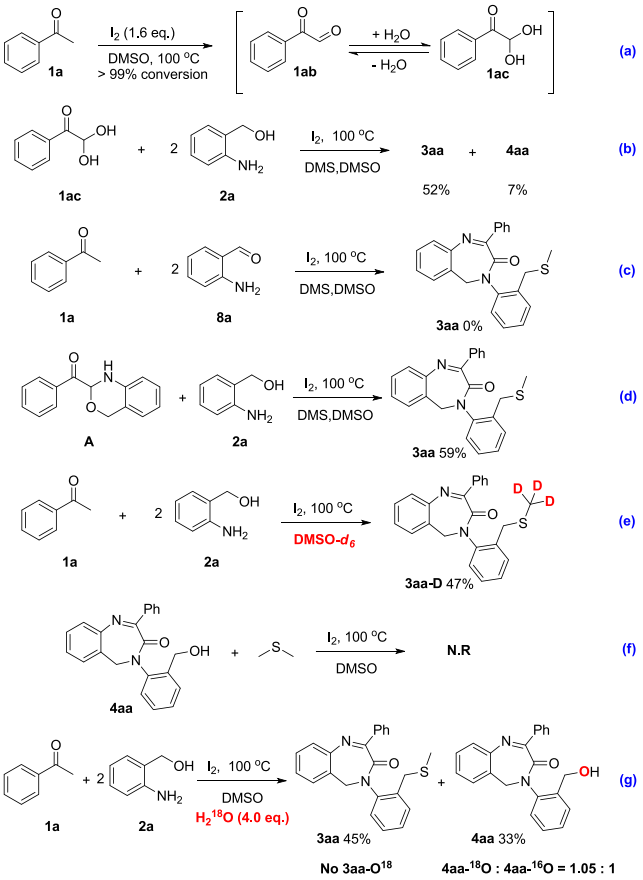
To gain insight into the mechanism of this novel formal [4 + 2 + 1] annulation reaction, a series of control experiments were conducted to better understand the reaction pathway. Initially, acetophenone **1a** reacted smoothly to give phenylglyoxal **1ab**

Scheme 4. Synthetic Utilities of the Current Protocol



and hydrated species **1ac** in quantitative yield via iodination and Kornblum oxidation (Scheme 5a). When hydrated species

Scheme 5. Control Experiments



1ac were mixed with **2a** under the optimized conditions, desired product **3aa** was obtained in 52% yield with product **4aa** in 7% yield (Scheme 5b). However, desired product **3aa** was not obtained when **2a** was replaced with **8a** (Scheme 5c), confirming that **8a** was not the intermediate in this four-component reaction. Meanwhile, pre-prepared substrate **A** reacted smoothly with substrate **2a** to afford product **3aa** in 59% yield (Scheme 5d). This result implied that **A** was an intermediate in this transformation. A deuterium-labeling experiment was also performed, affording **3aa-D** in satisfactory yield (Scheme 5e), which clearly confirmed that *in situ* generated DMS participated in this four-component reaction.

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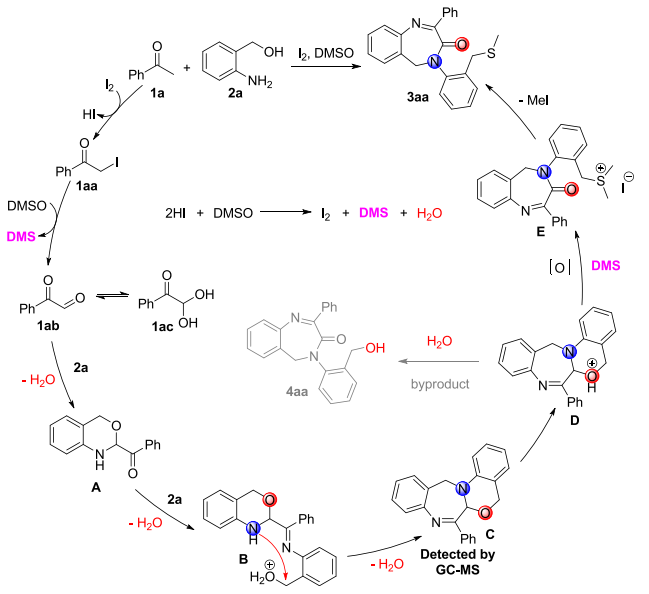
However, **4aa** could not be transformed into **3aa** under the optimized conditions (Scheme 5f). This indicated that **4aa** was a byproduct rather than an intermediate. To further study the source of oxygen in the target product, **1a** and **2a** were mixed under optimal conditions with the addition of $H_2{}^{18}O$ (4.0 equiv). However, no ^{18}O-labeled product (^{18}O-**3aa**) was detected, while ^{18}O-**4aa** was obtained in 33% yield (Scheme 5g). These results indicated that the oxygen atom of **3aa** was derived from 2-aminobenzyl alcohol (**2a**) via C−O bond cleavage.

On the basis of the current results and reported literature,[9,11,12,14] a plausible mechanism for this multicomponent reaction was proposed, as shown in Scheme 6.

Scheme 6. Proposed Mechanism



Phenylglyoxal **1ab** and corresponding hydrated species **1ac** are readily generated from acetophenone **1a** via iodination and Kornblum oxidation. Intermediate **1ab** then undergoes a [5 + 1] cycloaddition with 2-aminobenzyl alcohol **2a** to furnish the first cyclized intermediate **A**, which reacts with **2a** to give imine intermediate **B**. Intermediate **B** then undergoes intramolecular nucleophilic substitution to form the second cyclized intermediate **C** (detected by GC-MS), which is subsequently activated by acid to form intermediate **D**. A ring-opening process then occurs between intermediate **D** and DMS, followed by oxidation to furnish intermediate **E**. Finally, intermediate **E** undergoes elimination of MeI to give desired product **3aa**. Furthermore, byproduct **4aa** can be obtained from intermediate **D** and H_2O through a similar process.

In summary, we have developed an iodine-promoted multicomponent reaction for the synthesis of diverse benzo[*e*][1,4]diazepin-3-ones under mild conditions. This work represents an efficient strategy for constructing seven-membered ring lactams. Furthermore, this novel protocol enriches the reactivity of 2-aminobenzyl alcohols to formal [4 + 2 + 1] annulations. Notably, mechanistic studies showed that a cascade dicyclization and ring-opening process might occur in the reaction. Further studies toward the construction of such medium-sized rings are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02789.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1937301 and 1937306 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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