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Metal-Free Ring Opening Cyclization of Cyclopropane Carbaldehydes and N-benzyl Anilines: An Eco-friendly Access to Functionalized Benzo[b]azepine Derivatives

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Abstract. Herein, we report a p-toluenesulfonic acid (PTSA) initiated mild and user-friendly ring opening/domino ring opening cyclization reaction (depends on substituent present in N-benzyl aniline) of cyclopropane carbaldehyde and N-benzyl aniline towards the formation of substituted 4-amino butanal/2,3-dihydro-1Hbenzo[b]azepine. The product dihydro-1*H*-benzo[b]azepine was also converted into the corresponding tetrahydro-1Hbenzo[b]azepine.

Keywords: cyclopropane carbaldehyde; *N*-benzyl aniline; metal-free ring opening cyclization; benzo[*b*]azepine

Nitrogen heterocycles are the unique class of cyclic structural frameworks present in various natural and non-natural products. In particular, benzo[*b*]azepine, a distinct class of seven-member *N*-heterocycles, exists as a pivotal structural segment in many molecules of biological and pharmaceutical importance.^[1] For instance, clomipramine, an antidepressant agent,^[1a] OPC-41061, a highly potent human vasopressin V₂-receptor antagonist,^[1b] and benazepril, an ACE inhibitor^[1c] are the representative examples of the drugs containing benzo[*b*]azepine as a cyclic core (Figure 1). Consequently, the construction of such heterocycles from simple precursors is always a major interest.



Figure 1. Drugs with benzo[b]azepine skeleton.

Over the years, cyclopropane has emerged as an inimitable three carbon building block in the arena of organic synthesis.^[2] Owing to their inherent ring strain, upon activation with an external agent like Lewis acid

(namely transition metal halides and triflates) or other transition metal catalyst, cyclopropane undergoes various cycloaddition, ring opening, rearrangement and ring expansion reactions towards the formation of diverse high-value open-chain and cyclic compounds.^[3] For example, Chan *et al.* synthesized 2,3-dihydro-1*H*-benzo[*b*]azepine via a gold-catalyzed rearrangement of 2-tosylaminophenyl cyclopropyl methanol.^[4a] Whereas, Wender et al. employed cyclopropyl imine and alkyne in rhodium catalyzed (5+2) cycloaddition reaction for the construction of azepine derivatives (Scheme 1).^[4b] In the last decade, the practitioners of organic chemistry have extensively explored varieties of metal catalyzed reactions of cyclopropane. Many of them have been successively utilized in the total synthesis as well.^[5]

Previous work; Metal catalyzed synthesis of azepine from cyclopropane Chan et al. Gold catalyzed rearrangement of cyclopropyl methanol



Wender et al. Rhodium catalyzed (5 + 2) cycloaddition of cyclopropyl imine and alkyne

This work; Metal free synthesis of azepine derivatives from cyclopropane



Scheme 1. Synthesis of azepine derivatives from cyclopropane.

Despite of the exciting explorations of various reactivities and their utilization, very often some Lewis acid catalyzed reactions of cyclopropane associated with many disadvantages like toxicity, hazardous handling, high cost and a trace amount of metal contamination in the final product.^[6] In pharmaceutical and biological grounds, the latter issue is a serious practical problem and thereby requires an additional time consuming and expansive metal removing step.^[6b] Moreover, their extreme moisture sensitivity often necessities the use of 4 Å molecular sieves as an additive. Hence, it is necessary to develop the discussed reactions of cyclopropane in mild and metal-free conditions.

Table 1. Optimization of the reaction conditions for the ring opening reaction^{a)}

Ar Ar	HO + HN→	OMe	DCM, rt	Ar CHO Bn OMe
1a		О́Ме 2а Аг=.	4-methoxy pheny	I 3aa OMe
entry	PTSA	solvent	time (h)	yield (%) ^{b)}
	(mol%)			
01	-	toluene	24	22
02	20	toluene	24	58
03	20	benzene	24	56
04	20	ACN	15	c.m. ^{c)}
05	20	MeOH	07	c.m. ^{c)}
06	20	EtOH	07	c.m. ^{c)}
07	20	THF	12	c.m. ^{c)}
08	20	DCE	18	55
09	20	DCM	15	64
10	30	DCM	15	60
11	50	DCM	12	48

^{a)}Reactions were carried out with 1 equiv of **1a** and 1 equiv of **2a**. ^{b)}Isolated yield. ^{c)}c.m. = complex mixture.

In the contemporary metal-free reactions of cyclopropane, one of the impressively achieved ways is Bronsted acid catalytic activation.^[7] Where the hydrogen bonding of acceptor functionality with the Bronsted acid results the vicinal C-C bond polarization and therefore, makes the cyclopropane susceptible towards nucleophilic ring opening reaction. With the Bronsted acid catalytic activation, in a recent seminal report, Moran *et al.* have displayed a cyclopropane ring opening reaction by trimethoxybenzene, catalyzed by triflic acid in hexafluoroisopropanol.^[7b] Very recently, Kerr *et al.* reported a ring opening reaction of cyclopropane-1,1-dicarboxylate with indole via hydrogen bonding activation.^[7c]

On the other hand, commercially inexpensiveness, strong hydrogen bonding ability, ease of handling, and the existence of a rich body of literature on Bronsted acid catalysis,^[8] drive us to test the ability of PTSA on the activation of cyclopropane carbaldehyde. Thereby, on the basis of discussed literature reports, and our previous works on metal-catalyzed reactions of cyclopropane,^[9] we anticipated that the cyclopropane carbaldehyde can be activated by PTSA and would undergo ring opening reaction with a strong nucleophile like *N*-benzyl aniline. Afterwards, the formed open chain compound may undergo a Friedel-Crafts type reaction to form 2,3-dihydro-1*H*-benzo[*b*]azepine. More importantly, the presence of

PTSA in monohydrate form allowed us to perform all the designed reactions in open flask.

In the beginning, cyclopropanecarbaldehyde (1a) and N-benzyl dimethoxy aniline (2a) were chosen as model substrates to obtain the optimal condition for the ring opening reaction (Table 1). In the presence of PTSA, **1a** and **2a** were exposed in various solvents. Alcoholic solvents like methanol and ethanol gave a complex reaction mixture. Formation of the complex mixture was also found in acetonitrile (ACN) and tetrahydrofuran (THF). A good yield was acquired in benzene, toluene, dichloromethane (DCM), and dichloroethane (DCE) solvent. Among them for the short reaction time, DCM was adopted as the solvent of choice. To probe the equitable mol% of PTSA, we carried out the described reaction with various mol% of PTSA. On increasing the PTSA loading from 20 mol% to 50 mol% lead to decrease the reaction time and yield as well. Consequently, these results drive un to choose 20 mol% PTSA in DCM solvent as an optimal reaction condition.



Scheme 2. Substrate scope evaluation for the ring opening reaction: Unless otherwise specified, all reactions were carried out in DCM at rt with 1 equiv of 1 and 1 equiv of 2 in presence of PTSA (20 mol %). Isolated yields are reported.

Having the optimized condition in hand, we explored the substrate scope and limitation of the ring opening reaction (Scheme 2). To evaluate the substrate scope with respect to *N*-benzyl aniline, a range of *N*-benzyl anilines bearing different aromatic rings were employed in the ring opening reaction. A good yield

was provided by N-benzyl aniline bearing 3,4dimethoxy phenyl (2a), 4-methoxyphenyl (2b), and 3group. N-benzyl methoxyphenyl (2c) aniline containing phenyl ring (2d) engendered the desired product 3ad with longer reaction time. Whereas, Nbenzyl aniline (2e) having 4-nitrophenyl group did not participate in the reaction. This may be due to the lowering of nucleophilicity by very high electron withdrawing ability of the nitro group. However, Naniline with 4-fluorophenyl benzvl (**2I**), 4bromophenyl (2m) and 4-iodophenyl (2n) ring were comfortably converted to their corresponding ring opened product with a good yield.

To check the effect of benzyl group on the said reaction, we employed two different N-benzyl anilines (2f, 2g) containing 4-bromo benzyl and 2,3-dimethoxy benzyl group. However, in both cases, reaction rate, and yield were similar. Therefore, these results revealed that the substitution on the benzyl group has no such considerable effect on the titled reaction. In order to examine the effect of aryl substituent on cyclopropane, we executed a series of reactions of Nbenzyl-4-methoxyaniline (2b) with a range of cyclopropane carbaldehydes (1a-1h). Cyclopropane bearing more electron donating group like methylenedioxyphenyl (1b) furnished the desired product with a lower yield. Perhaps this is due to the presence of highly electron donating substituent which makes the cyclopropane carbaldehyde vulnerable to decomposition. The same outcome was also noticed for cyclopropane carbaldehyde bearing a 2-naphthyl substituent (1c). Cyclopropane (1d) bearing 4-(benzyloxy)phenyl group gave a satisfactory yield. The best yield was accomplished with the cyclopropane (1e) containing the tolyl group. Cyclopropane with simple phenyl ring (1f) and cinnamyl group (1h) also gave good yield whereas, cvclopropane (1g) with 4-chlorophenvl ring furnished the product in longer reaction time. This is because of the electron withdrawing ability of choro substituent; making the respective cyclopropane carbaldehyde less reactive towards nucleophilic ring opening.



Scheme 3. Towards cyclization of the ring-opened product.

Having synthesized a range of ring-opened product, we conceived the possibility of an intramolecular Friedel-Crafts type reaction between the N-aryl and aldehyde functionality in 3 towards the formation of benzo[b]azepine moiety (Scheme 3A). Our initial trial with ring opened compound 3ab bearing 4methoxyphenyl ring was not accomplished (Scheme 3A). However, we could attain the intended compound with the ring-opened product 3aa bearing 3,4dimethoxy phenyl ring. Eventually, the efficient conversion of 3ac into the homologous benzo[b]azepine **4ac** manifested that the presence of a methoxy substituent at 3-position of phenyl ring is essential for the cyclization to happen. After this successful cyclization, to achieve the domino ring opening-cyclization reaction, we carried out both steps in one pot. Gratifyingly, with this domino decorum, the desired **4aa** was synthesized in a satisfactory yield (Scheme 3B). It is important to note that the addition of 1.2 equivalent of PTSA at a time resulted the decomposition of a considerable amount of cyclopropane carbaldehyde. Therefore, firstly 0.2 equivalent of PTSA was added to complete the ring opening process followed by addition of the remained amount of PTSA (1 equivalent) to fulfill the cyclization process.



Scheme 4. Evaluation of the substrate scope for domino ring opening-cyclization reaction: Unless otherwise specified,

all reactions were carried out in DCM at rt with 1 equiv of 1 and 1 equiv of 2 in presence of PTSA (120 mol %). Isolated yields are reported.

Having established the domino protocol, we evaluated the scope and limitation of other substrates in this process, and the outcomes are depicted in scheme 4. Among the various cyclopropanes, cyclopropanes (1a and 1f) bearing 4-methoxyphenyl and phenyl group gave the good yield, as obtained in the ring opening reaction. However, cyclopropane having methylenedioxyphenyl (1b) and 4-benzyloxy phenyl ring (1d) afforded their respective cyclic product in a lower yield. Tolyl substituted cyclopropane (1e) provided a very clean reaction towards the formation of the desired product 4ea in a better yield. Prolonged reaction time was noticed for the cyclopropane bearing 4-chlorophenyl ring (1g). To check the scope for N-benzyl anilines, a range of Nbenzyl anilines (2h-2k) bearing 3,4-dimethoxy substituted phenyl ring were engaged in the domino reaction. But no such pronounced effect was noticed. Starting with a fused cyclopropane carbaldehyde (1i), benzo[b]azepines **4ia** containing a fused [6-7-6] tricyclic framework was constructed in a good yield.



Scheme 5. Reduction of 4aa.



Scheme 6. Stereospecificity of the ring opening reaction.

After the successful preparation of a range of 2,3dihydro-1*H*-benzo[*b*]azepines, the 2,3-dihydro-1*H*benzo[*b*]azepine **4aa** was converted into the corresponding 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine derivative **5aa** through the reduction with LAH/FeCl₂ mixture (Scheme 5).^[10]

On the basis of other literature reports and our observations, we sketched a plausible mechanism as shown in scheme 7. Initially, PTSA interacts with the cyclopropane carbaldehyde 1 to form an activated intermediate A. Intermediate A encountered a

nucleophilic ring opening with N-benzyl aniline 2 to form the open chain compound 3. Afterward, the aldehyde functionality of **3** get activated by PTSA to form intermediate B which underwent an intramolecular Friedel-Crafts type reaction to produce the alcohol **D** via formation of **C**. Finally, **D** converted into the desired compound 4 by dehydration. To investigate the stereospecificity of the ring opening process, enantioenriched an cyclopropane carbaldehyde 1f was employed in the mentioned reaction (Scheme 6). Formation of the enantioenriched product **3fb** established that the reaction proceeds in an almost stereospecific manner.



Scheme 7. Plausible mechanism

In conclusion, we displayed a metal-free ring opening and cyclization reaction of cyclopropane carbaldehyde and N-benzyl aniline, mediated by commercially inexpensive PTSA. Depends on the substituent present in aryl ring of N-benzyl aniline, the process provides substituted 4-amino butanal or 2,3dihydro-1H-benzo[b]azepine via ring opening or domino ring opening-cyclization pathway. Happening of the reaction in an open-flask exhibit the userfriendliness of the process. Furthermore, the product 2,3-dihydro-1*H*-benzo[*b*]azepine was also converted to a high-value structural scaffold, like 2,3,4,5tetrahydro-1*H*-benzo[*b*]azepine derivative. Development of the asymmetric version of this protocol and application in the total synthesis of the natural product are underway in our laboratory.

Experimental Section

Representative procedure for ring opening reaction of cyclopropane carbaldehyde (1) and N-benzyl aniline (2)

To a round-bottom flask equipped with a magnetic stir bar was charged with PTSA (0.05 mmol, 0.2 equiv). A DCM (2.8 mL) solution of cyclopropane carbaldehyde (0.28 mmol, 1 equiv) and *N*-benzyl aniline (0.28 mmol, 1 equiv) was added and stirred at room temperature until completion of the reaction (as monitored by TLC). The solvent was evaporated on a rotary evaporator. The crude mixture was further purified by column chromatography on silica gel with ethyl acetate/hexane as eluent.

Representative procedure for domino ring openingcyclization reaction of cyclopropane carbaldehyde (1) and N-benzyl aniline (2):

To a round-bottom flask equipped with a magnetic stir bar was charged with PTSA (0.05 mmol, 0.2 equiv). A DCM (2.8 mL) solution of cyclopropane carbaldehyde (0.28 mmol, 1 equiv) and *N*-benzyl aniline (0.28 mmol, 1 equiv) was added and stirred at room temperature. After consumption of the starting materials, (as monitored by TLC) PTSA (0.28 mmol, 1 equiv) was added and stirred at room temperature. After completion of the reaction, the organic layer was diluted with DCM and washed with aqueous NaHCO₃ solution. The organic layer was dried over Na₂SO₄ and concentrated on a rotary evaporator. The crude mixture was further purified by column chromatography on silica gel with ethyl acetate/hexane as eluent.

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Adv. Synth. Catal. Year, Volume, Page - Page

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