Organic LETTERS

Letter

pubs.acs.org/OrgLett

2-Oxo-Driven N_2 Elimination Induced Decarbonylative Cyclization Reaction in Benzotriazoles to 6-Aminophenanthridines

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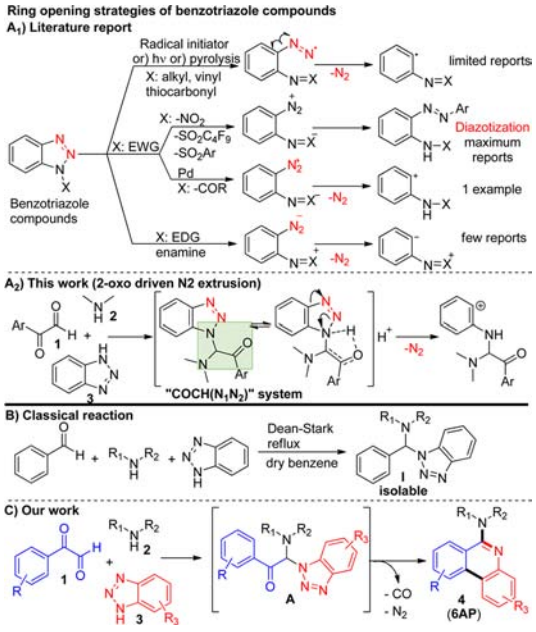
Supporting Information

ABSTRACT: An efficient functional group induced strategy for the synthesis of 6-aminophenanthridines (6AP) has been developed as a result of an in situ generated novel system "CO−CH(N_1N_2)". This reaction presents a new mode of N_2 extrusion in benzotriazoles that later result in decarbonylative cyclization to 6AP. This method offers an easier protocol for the synthesis of 6AP from readily available inexpensive substrates.

Several decades ago, Katritzky's group applied benzotriazoles as a synthetic auxiliary for the generation of several important heterocycles. Benzotriazole (BTA) has always been an intriguing substrate due to its multiple roles and modes in chemical transformations and important applications in biology.[1] However, due to its high structural stability and an innate tendency to exist as diazonium salt instead of diazo, not much research has been conducted on benzotriazoles involving ring-opening chemistry.[2c] As shown in Scheme 1 (A_1) different ring-opening strategies on BTA can be submersed in three categories. On one hand, in the presence of radical initiators[2]/irradiation[3] or on pyrolysis,[4] BTA undergoes N_2 extrusion in a free-radical approach. This is perhaps most common strategy among nitrogen elimination reactions on BTA. On the other hand, ring opening on BTA containing an N-substituted electron-withdrawing group proceeds in two ways. Many reports have shown that ring-opening methods are established through diazonium salts, and these methods have been applied for the generation of azobenzenes.[5] Under the same umbrella, Nakamura et al. reported the N_2 elimination in BTA in a way to generate aryl electrophile that later reacted with various acetylenes to generate indoles.[6] Lastly, benzotriazoles that possess donating groups, like enamine, have been reported to undergo N_2 loss in a reverse manner resulting in production of aryl nucleophile which ultimately reacts with either electrophiles or proton (Scheme 1 (A_1), literature report).[7] However, due to the absence of adequate literature on functional group induced ring-opening reactions in BTA, not much work has been reported in this area. In this direction, we present the first report of a functional group induced ring opening/N_2 elimination reaction on an in situ generated valuable system "CO−CH(N_1N_2)" (Scheme 1 (A_2)). Herein, we present the new face of BTA ring-opening reactions, and we have applied the same for the generation of 6-aminophenanthridines (6AP). The phenanthridine entity represents an important structural unit found in natural products and in biologically relevant compounds.[8−10] In addition, comparison of our in situ generated system (A) with the isolable compound (I) justifies the unprecedented role of the 2-oxo group toward generation of 6AP (Scheme 1 (B,C)). As a result, the present work describes 2-oxo-driven N_2 extrusion on a novel in situ generated BTA system that ultimately catalyzed the cyclization, followed by a decarbonylation reaction to 6AP.

Scheme 1. Summary of Work



Received: September 17, 2015
Published: November 2, 2015

DOI: 10.1021/acs.orglett.5b02699
Org. Lett. 2015, 17, 5562−5565

We commenced our study by reacting phenyl glyoxal **1a** (0.460 mmol) with morpholine **2a** (0.460 mmol) and benzotriazole **3a** (0.460 mmol) in toluene (2 mL) at 60 °C (entry 1, Table 1). To our surprise, 4-(phenanthridin-6-yl)morpholine **4a** was isolated in 17% yield along with 58% of α-ketoamide **5a**. The same reaction, when performed at room temperature, failed to produce 6AP (entry 2). Upon increasing the temperature to 80 °C, the yield of the desired product increased to 51% (entry 3). A further increase in temperature to 100 °C showed a negative effect on the isolation of the desired product (entry 4). In order to improve the yields of our reaction, we also screened our reaction in the presence of different copper salts at 10 mol % (entries 5–8). $CuBr_2$ was found to be the catalyst of choice for the generation of **4a** in 63% yield (entry 6). In addition, the effect of independently varying the concentrations of **2a**, **3a**, and metal salt was also studied (entries 9–14). Finally, we achieved the synthesis of the desired product in the best yields (71%, entry 11) when the reaction was performed with phenylglyoxal **1a** (0.460 mmol), morpholine **2a** (0.506 mmol), benzotriazole **3a** (0.552 mmol), and $CuBr_2$ (10 mol %) in toluene at 80 °C for 3 h. This condition fortunately avoided the production of side product **5a**. Finally, we also observed that addition of external base (Et_3N, 1.0 equiv, entry 15) or reactions in the presence of organic oxidants (entries 16–18) had no effect on their yields.

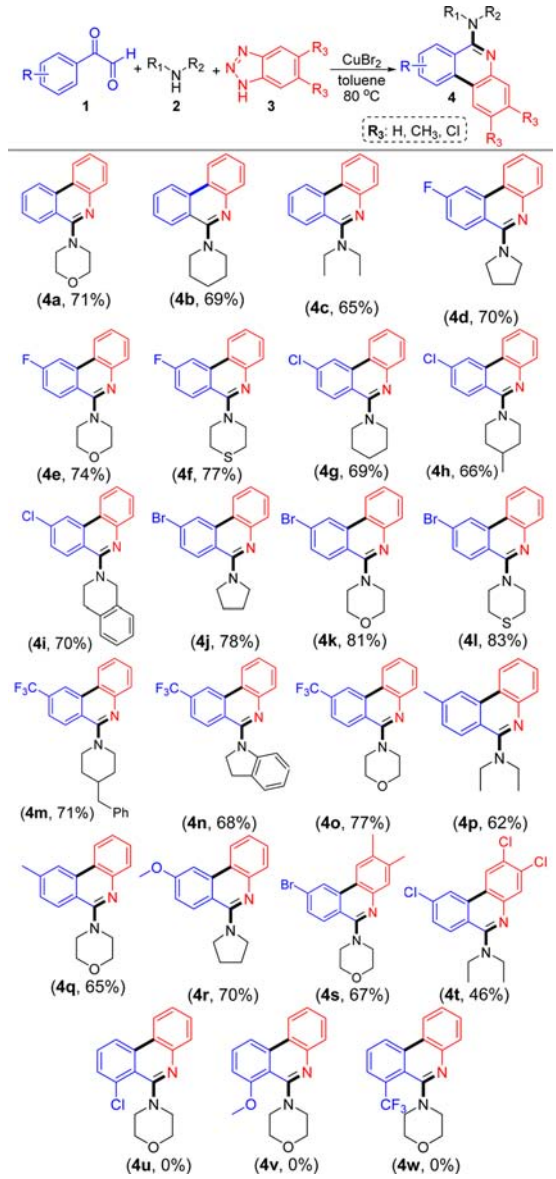
In order to exert a symmetric environment offered due to benzotriazoles and 2-oxoaldehydes (2OAs) in our reactions, we conducted different reactions under optimized conditions between *p*- and *o*-substituted 2-oxoaldehydes **1**, secondary amines **2**, and benzotriazoles **3** containing similar groups at the 4- and 5-positions to generate different 6APs (Scheme 2). As observed, the electronic environment of phenyl ring in 2OA has affected the yields of product to some extent. On the basis of our observations, the 2OAs bearing electron-withdrawing groups, for example, −F (**4d–f**), −Cl (**4g–i**), −Br (**4j–l**), $-CF_3$ (**4m–o**) afforded slightly higher yields in comparison to unsubstituted 2-oxoaldeydes (**4a–c**) and those containing electron-donating groups $-CH_3$ (**4p** and **4q**) and $-OCH_3$ (**4r**). However, reactions with *o*-substituted 2OAs failed to produce the desired product (**4u–w**). Looking to the nature of our reactions in accordance to the change in secondary amines, we observed a considerable effect in the yields of 6AP. Reactions with six-membered cyclic secondary amines produced better yields than the five-membered ones. In addition, cyclic amines having heteroatoms (S and O) afforded good yields compared to its

Table 1. Optimization of the Reaction[a]

entry	2a (equiv)	3a (equiv)	additive	temp (°C)	time (h)	yield[b] (%) 4a	5a
1	1	1		60	2	17	58
2	1	1		rt	2.5		82
3	**1**	**1**		**80**	**3**	**51**	**30**
4	1	1		100	3	45	52
5	1	1	CuBr (10)	80	3	55	<8
6	1	1	$CuBr_2$ (10)	80	3	63	
7	1	1	$Cu(OAc)_2$ (10)	80	3	59	<10
8	1	1	$Cu(OTf)_2$ (10)	80	3	52	12
9	1	1.2	$CuBr_2$ (10)	80	3	65	
10	1	1.5	$CuBr_2$ (10)	80	3	65	
11	**1.1**	**1.2**	**$CuBr_2$ (10)**	**80**	**3**	**71**	
12	1.2	1.2	$CuBr_2$ (10)	80	3	71	
13	1.1	1.2	$CuBr_2$ (5)	80	3	67	<10
14	1.1	1.2	$CuBr_2$ (15)	80	3	71	
15[c]	1.1	1.2	$CuBr_2$ (10)	80	3	71	
16	1.1	1.2	IBX (10)	80	24	31	
17	1.1	1.2	NIS (10)	80	24	27	
18	1.1	1.2	PIFA (10)	80	24	34	

[a]Reaction conditions: **1a** (0.460 mmol), **2a** (0.506 mmol), **3a** (0.552 mmol), $CuBr_2$ (10 mol %), and toluene (2 mL); [b]Isolated yields [c]Reaction in the presence of 1.0 equiv of Et_3N.

Scheme 2. Scope of the Reaction[a]



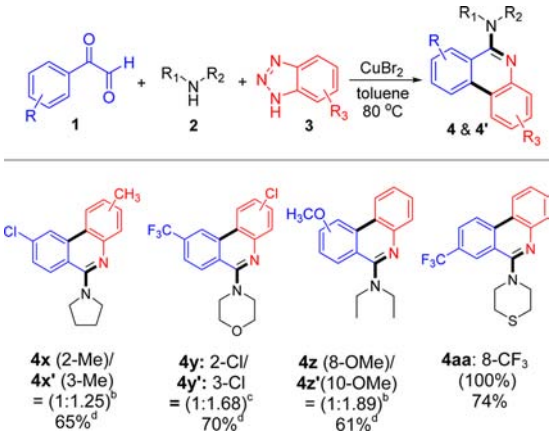
[a]Reaction conditions: **1** (0.460 mmol), **2** (0.506 mmol), **3** (0.552 mmol), $CuBr_2$ (10 mol %), and toluene (2 mL); at 80 °C and 3–6 h.

DOI: 10.1021/acs.orglett.5b02699
Org. Lett. 2015, 17, 5562–5565

analogous amines. Further, the reactions with open aliphatic amines procured slightly lower yields (**4c** and **4q**). Furthermore, reactions conducted with benzo-fused secondary amines like THIQ (**4i**) and indolines (**4n**) also worked well in our system. Lastly, reactions with different BTAs, viz., 4,5-dimethyl- (**4s**) and 4,5-dichlorobenzotriazoles (**4t**), endured the reaction conditions and afforded comparable yields.

Later, to interpret the regioselectivity observed in the synthesis of 6APs, a set of reactions was conducted between 2OAs, secondary amines, and benzotriazoles as shown in Scheme 3.

Scheme 3. Scope of the Reaction[a]

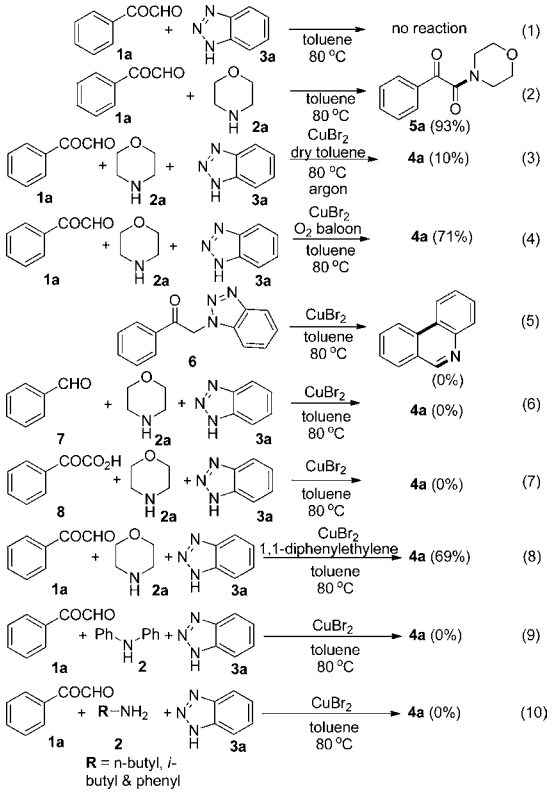


[a]Reaction conditions: **1** (0.460 mmol), **2** (0.506 mmol), **3** (0.552 mmol), $CuBr_2$ (10 mol %) and toluene (2 mL), at 80 °C and 3−6 h time. [b]Ratio estimated by ^1H NMR. [c]Ratio estimated by HPLC. [d]Overall yield of both regioisomers.

Monosubstituted benzotriazoles could produce compatible regioselectivity with respect to both isomers of 6AP (**4x**, **4x′** and **4y**, **4y′**). Among the two reactions conducted with *m*-substituted 2-oxoaldehydes, 3-methoxy-2-oxoaldehyde produced regioisomers (**4z**, **4z′**), whereas the reaction with 3-CF_3-substituted 2-oxoaldehyde selectively afforded a single isomer. As observed, 2OAs generally produced better selectivity than the benzotriazoles.

In order to probe the intrinsic mechanism of 6AP synthesis, we performed a few controlled experiments (Scheme 4). Experiment 1, conducted between **1a** with **3a** in toluene, failed to generate any reaction, proving the low nucleophilicity of BTA toward 2OA in the absence of a secondary amine. Similarly, in experiment 2, the generation of *α*-ketoamide **5a** in the absence of BTA clearly highlighted the role of BTA as nucleophile that prevents the aerobic oxidation of 2-oxoiminium generated in situ in our system. In experiment 3, we observed lower yields under dry conditions in argon atmosphere, and in experiment 4, the same yields were obtained as in the optimized results in the presence of an oxygen atmosphere. These two experiments together pointed toward the adequate importance of atmospheric oxygen in 6AP synthesis. In experiment 5, compound **6** was found unreacted when tested against our reaction conditions. These findings undoubtedly emphasize the need for a CO−CH(N_1N_2) structural unit for the reaction to occur. When our original reaction was performed with normal aldehyde/2-oxoacid, no product was observed (experiments 6 and 7). These observations certainly indicated the crucial role of the 2-oxo group in the synthesis of 6AP. In addition, experiment 7 clearly assigned the importance of 2OA to trigger the reaction

Scheme 4. Control Experiments



through the initial formation of the 2-oxoiminim ion. Since TEMPO could individually react with 2OA,[11] we preferred to conduct experiment 8 in the presence of 1,1-diphenylethylene[12] in order to judge the reaction pathway. As evident in experiment 8, the free-radical pathway in our reaction can be excluded. Finally, absence of the desired products in experiments 9 and 10 indicated that neither diphenyl-substituted amines nor primary amines were the substrate of choice for our reactions. Perhaps diphenylamine failed due to low nucleophilicity and primary amines from a lack of iminium ion formation.

On the basis of the above results, a plausible mechanism for the formation of 6AP was presented in Figure 1. Initially, 2OA **1** combines with secondary amine **2** to produce 2-oxoiminium ion (**2OI**). Under a basic environment, BTA generates its nucleophilic unit (**nBt**), which attacks the 2-oxoiminium ion and generates an expected tricomponent *α*,*α*-diamino carbonyl

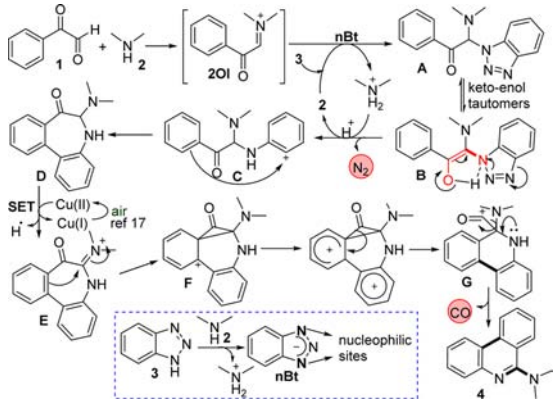


Figure 1. Plausible Mechanism.

DOI: 10.1021/acs.orglett.5b02699
Org. Lett. 2015, 17, 5562−5565

adduct **A**. Its enolic form **B** instantaneously produces reactive aryl electrophile **C** by N_2 elimination, possibly through a 5 membered hydrogen-bonding cycle. Later, it undergoes electrophilic substitution and produces cyclic product **D** that immediately produces a second iminium ion **E** under a Cu/air system.[13] It later rearranges to form another intermediate **F**, which ultimately produces 6AP **4** by decarbonylation from **G**. In order to justify our proposed reaction mechanism, we performed LC-ESI-MS experiments on three different representative reactions (for details, see the Supporting Information). We successfully traced independent masses of different intermediates, viz., **2OI**, **D**, and **E**. These studies confirmed that the reaction is feasible through the initial formation of a 2-oxoiminium ion (**2OI**) and the cyclization by N_2 extrusion to intermediate **D** followed by secondary iminium ion **E** generation that ultimately undergoes decarbonylation to 6AP **4**.

In conclusion, we have established a new concept in BTA-based ring-opening chemistry and successfully applied the same concept for the generation of different secondary amine substituted phenanthridines (6AP) from readily available substrates. Further studies related to the application of this synthesis for other heterocycles are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02699.

Experimental procedures, ^1H, ^{13}C, spectra, LC-ESI-MS data, and characterization of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.B. and A.K. thank CSIR and UGC, respectively, and also thank AcSIR. This work was generously supported by CSIR network project through grant no. BSC-0108. IIIM communication no. IIIM/1854/2015.

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DOI: 10.1021/acs.orglett.5b02699
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