Organic LETTERS

Letter

pubs.acs.org/OrgLett

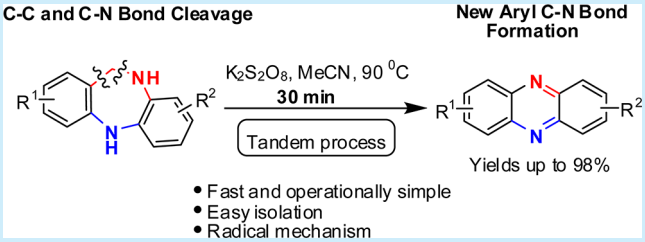
Transition-Metal-Free Tandem Oxidative Removal of Benzylic Methylene Group by C−C and C−N Bond Cleavage Followed by Intramolecular New Aryl C−N Bond Formation under Radical Conditions

Joydev K. Laha,* K. S. Satyanarayana Tummalapalli, and Ankur Gupta

Department of Pharmaceutical Technology (Process Chemistry), National Institute of Pharmaceutical Education and Research, S. A. S. Nagar, Punjab 160062, India

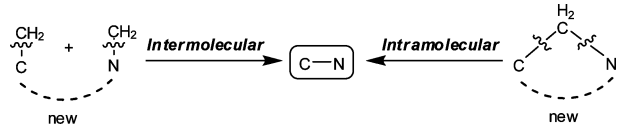
Supporting Information

ABSTRACT: A novel tandem oxidative conversion of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines to phenazines has been achieved under transition-metal-free, mild conditions using $K_2S_2O_8$ or DDQ as the oxidizing agent. The transformation proceeds through oxidative removal of a benzylic methylene group by C−C and C−N bond cleavage followed by a new aryl C−N bond formation under radical conditions.



Carbon−carbon or carbon−nitrogen bonds are omnipresent in organic compounds. While the formation of these bonds merits extensive discussion, the chemoselective cleavage of these bonds is still a difficult objective. Although a handful of reports are available for the oxidative cleavage of C−C[1] and C−N[2] bonds, harsh conditions and the use of expensive and toxic metals in combination with oxidants have traditionally been required. Despite the fact that cleavage of both C−C and C−N bonds in a single synthetic operation could present a significant challenge, the cleavage of these bonds have been successfully demonstrated though limited to a few reports.[3] The challenge would further be exacerbated with a desire to form a new bond at the expense incurred for the cleavage of two bonds (Scheme 1).

Scheme 1. Cleavage of Two Bonds and Subsequent Formation of a New Bond



Unlike intermolecular reaction, cleavage of C−C and C−N bonds followed by formation of a new C−N bond in an intramolecular strategy could account for net loss of a methylene unit. To achieve this goal, the following points were taken into consideration: (a) a judicious choice of substrate to demonstrate the proof-of-concept and (b) choice of oxidant that could enable the transformation under metal-free conditions. Nonetheless, the cleavage of C−C and C−N bonds with the formation of a new C−N bond under one set of conditions would be a formidable task.

Very recently, we have developed an expedient domino synthesis of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines that are otherwise difficult to obtain by literature methods.[4] The methodology provided a workable access to various substituted 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines for a general structure−activity relationship study. In this context, we had an opportunity to demonstrate the proof-of-concept on 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines containing a cyclic secondary benzylamine moiety.

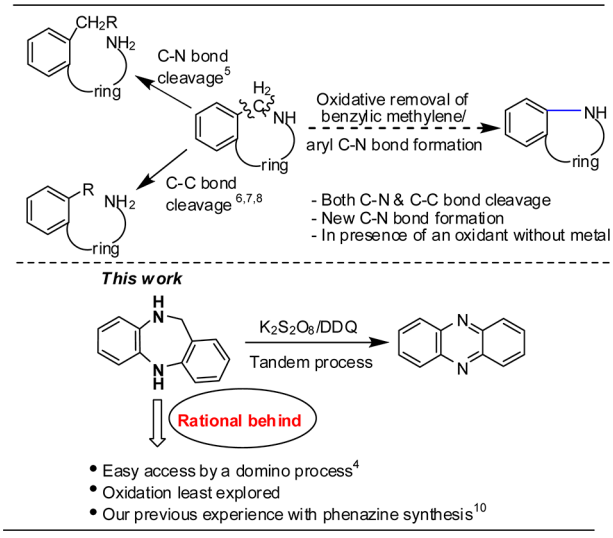
The cleavage of the CH_2−N(aryl) bond in cyclic secondary benzylamines is limited to a few reports (Scheme 2).[5] While direct cleavage of CH_2−C(aryl) bond is unprecedented, oxidation at the benzylic position is reported to give imines,[6] benzamides,[7] or nitrones,[8] which on subsequent synthetic transformation could cleave the CH_2−C(aryl) bond. In particular, the oxidation of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines is limited to a study only, wherein a few imines have been prepared by oxidation with MnO_2 under basic conditions.[9] Removal of the benzylic methylene unit in cyclic secondary benzylamines by cleavage of both CH_2−N(aryl) and CH_2−C(aryl) bonds is yet to be reported. We envisaged that oxidative removal of the benzylic methylene unit by cleavage of C−C and C−N bonds in cyclic secondary benzylamine, and subsequent new aryl C−N bond formation, would give ample opportunities to synthesize demethylenated heterocycles from substrates containing a cyclic secondary benzylamine moiety.

Herein, we describe a novel oxidative conversion of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines to phenazines[10] using $K_2S_2O_8$ or DDQ as the oxidizing agent under mild, metal-free conditions. The conversion proceeds through a tandem process involving oxidative removal of the benzylic methylene group by

Received: June 18, 2014

   dx.doi.org/10.1021/ol501766m | *Org. Lett.* XXXX, XXX, XXX−XXX

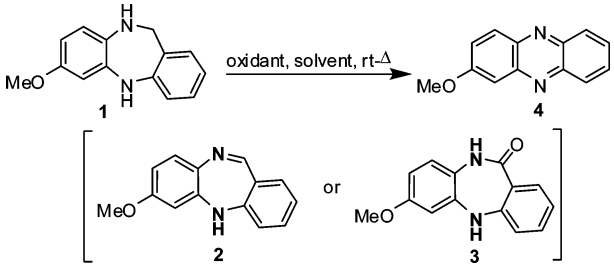
Scheme 2. C−C and C−N Bond Cleavage in Cyclic Secondary Benzylamines



C−C and C−N bond cleavage followed by a new aryl C−N bond formation.

Unlike the oxidation of **1** and MnO_2 under basic conditions,[9] the oxidation with MnO_2 in acetonitrile under neutral conditions did not give the expected imine **2**, and an insignificant conversion of **1** to product was observed (Table 1, entry 1). $K_2S_2O_8$ is a cheap, environmentally friendly powerful oxidant and has been found useful for C−C or C−N bond cleavage.[11] However, oxidative cleavage of C−C or C−N bond in cyclic secondary benzylamines using $K_2S_2O_8$ is beyond our knowledge.

Table 1. Optimization of $K_2S_2O_8$ Oxidation of Dibenzodiazepine 1 to Phenazine 4[a]



entry	oxidant	solvent	temp (°C)	yield[b] (%)
1	MnO_2	MeCN	25	0
2[c]	$K_2S_2O_8$	MeCN	25	48
3	$K_2S_2O_8$	MeCN	25	85
4[d]	$K_2S_2O_8$	MeCN	90	90
5	$KHSO_5$	MeCN	90	46
6	DDQ	MeCN	90	88
7	Ag_2O	MeCN	90	0
8[e]	$K_2S_2O_8$	MeCN	90	87
9[f]	$K_2S_2O_8$	solvents	90	0
10	$K_2S_2O_8$	anhyd MeCN	90	90
11[g]	$K_2S_2O_8$	MeCN	90	trace

[a]Dibenzodiazepine **1** (0.25 mmol), oxidant (0.50 mmol), solvent (4 mL, 160 mM), 25 °C, 6 h. [b]Isolated yield. [c]$K_2S_2O_8$ (0.25 mmol). [d]30 min. [e]20 mol % AgOAc. [f]Other solvents used: DCE, DMF, THF, MeOH, CCl_4, etc. [g]In the presence of a free-radical scavenger (0.25 mmol) such as ascorbic acid or BHT.

Treatment of dibenzodiazepine **1** with 1 equiv of $K_2S_2O_8$ in acetonitrile at room temperature did not give imine **2** or amide **3**; rather, phenazine **4** was isolated in 48% yield (entry 2). The formation of **4** could be explained by oxidative removal of the benzylic methylene unit followed by a new aryl C−N bond formation. Nonetheless, the tandem oxidative conversion of dibenzodiazepine **1** to phenazine **4** demonstrates a novel synthetic application of secondary benzylamine oxidation by $K_2S_2O_8$. Further experimentation was carried out to optimize the yield of phenazine **4**. When **1** was treated with 2 equiv of $K_2S_2O_8$ at room temperature, the yield of **4** was improved significantly (85% yield, entry 3). At an elevated temperature (90 °C), the progress of the reaction is faster and the reaction is complete in 30 min with a comparable yield (90% yield) of phenazine **4** (entry 4). Noticeably, oxidation of **1** with 2 equiv of $KHSO_5$[12] under similar conditions gave phenazine **4** only in 46% yield (entry 5). DDQ[13] demonstrated similar oxidizing efficiency as that of $K_2S_2O_8$, affording phenazine **4** in 88% yield (entry 6). While Ag_2O[14] is not effective for the conversion of **1** to **4**, use of a catalytic amount of AgOAc in the presence of $K_2S_2O_8$[15] produced phenazine **4** in 87% yield (entries 7 and 8). Replacing MeCN with other solvents was futile (entry 9). This experiment indicated that the oxidation is very specific to the use of MeCN as solvent. Anhydrous MeCN also gave the same result as that of analytical reagent-grade MeCN (entry 10). The oxidation of dibenzodiazepine **1** was ineffective when the reaction was carried out in the presence of a free radical scavenger ascorbic acid or BHT (3,5-di-*tert*-butyl-4-hydroxytoluene), which indicated that the oxidation could occur under radical conditions (entry 11).

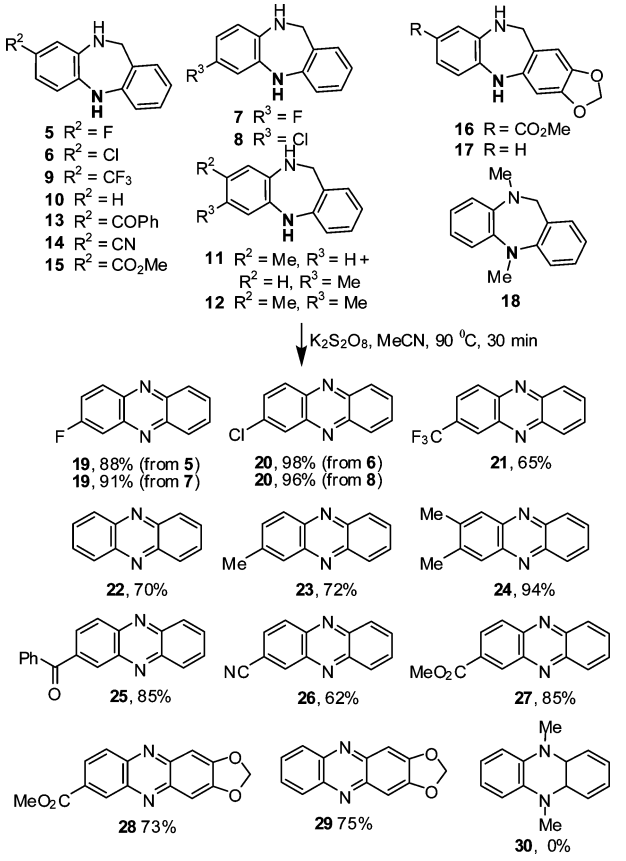
Eventfully, various substituted 10,11-dihydro-5H-dibenzo-[*b*,*e*][1,4]diazepines **5**−**16**,[4] **17**, and **18**[4] were found to undergo oxidative conversion to phenazines **19**−**20**, **21**−**22**,[10] **23**−**25**, and **26**−**29**[10] (except **18**) in good to excellent yields under the optimized conditions as shown in Scheme 3. Notably, various functional groups irrespective of their nature, whether electron-donating or -withdrawing, were tolerated under the conditions. For example, fluoro-, chloro-, trifluoromethyl-, or methylenedioxy-substituted dibenzodiazepines were converted to their corresponding phenazines. More importantly, the neutral oxidation condition makes this oxidative conversion useful, especially for the substrates that bear an acid- or a base-sensitive functional group. The functional groups such as cyano, ester, or ketone were found compatible under the optimized condition. Interestingly, complete regiocontrol was observed in the oxidation of dibenzodiazepines **16** and **17** to their corresponding phenazines. However, attempted oxidation of *N*,*N*-dimethyldibenzodiazepine **18** to dihydrophenazine **30** was unsuccessful.

As DDQ demonstrated a similar oxidizing effect as that of $K_2S_2O_8$ in the optimization study, we investigated the substrate scope for the DDQ oxidation and compared the oxidizing efficiency with $K_2S_2O_8$ (Scheme 4). While the oxidation efficiency of DDQ was comparable in the synthesis of phenazines **22**,[10] **25**, **26**,[10] and **27**[10] from their corresponding dibenzodiazepines, reduced yields were observed in the synthesis of phenazines **20** and **24**. In the latter cases, the formation of their corresponding imines, as evidenced from their GC−MS data, may account for the quantitative transformation of starting materials. Isolations of the imines by silica column chromatography were successful, but the imines degraded quickly before analytical data could be collected.

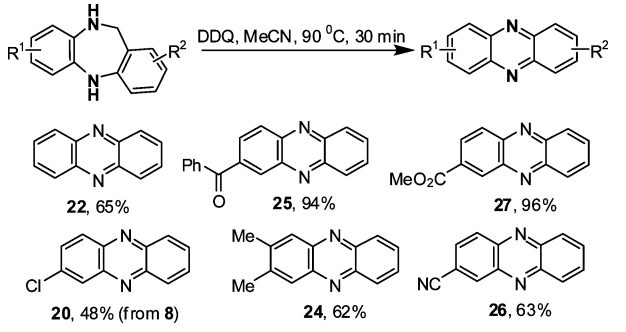
The mechanism for the oxidative conversion of dibenzodiazepines to phenazines is unclear. However, the following mechanism is proposed on the basis of limited study to understand

dx.doi.org/10.1021/ol501766m | *Org. Lett.* XXXX, XXX, XXX−XXX

Scheme 3. Oxidation of Various Substituted Dibenzodiazepines with $K_2S_2O_8$ to the Synthesis of Phenazines



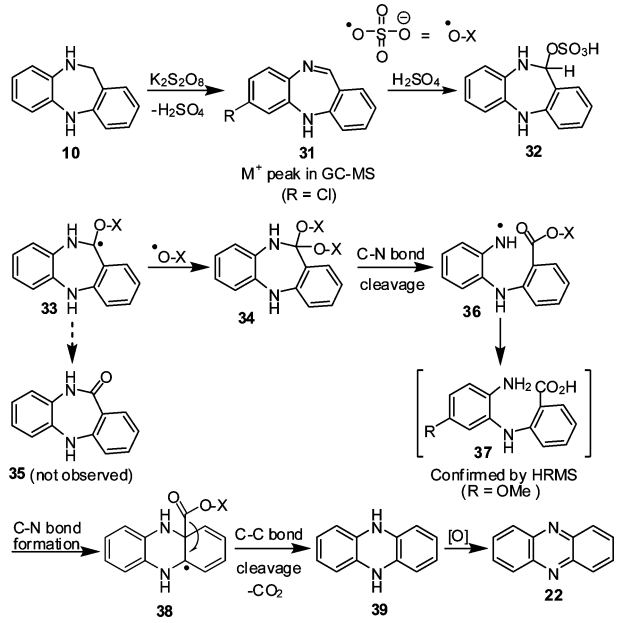
Scheme 4. Oxidation of Dibenzodiazepines to Phenazines by DDQ



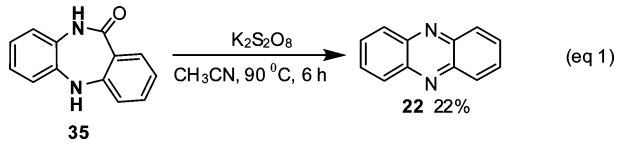
the mechanism (Scheme 5). The dibenzodiazepine **10** could be oxidized at the benzylic position to form imine **31**.[16] Addition of H_2SO_4, generated in situ from $K_2S_2O_8$ in the oxidation of **10** to **31**, to the imine **31** by an ionic mechanism[17] could form **32**. Abstraction of H• at the benzylic position in **32** could form a more stable benzyl radical **33**. Next, addition of sulfate radical anion ($SO_4^{\bullet-}$) to **33** followed by cleavage of C−N bond in the presence of acetonitrile would give an open-ring aminyl radical **36**. Attack of aminyl radical **36** onto the arene ring could give a resonance-stabilized aryl radical **38**,[17] which upon decarboxylation[18] via β-elimination could give dihydrophenazine **39**. Subsequent oxidation of **39** could give phenazine **22**.

Several experiments were carried out to gain insights into the reaction mechanism. The evidence of the formation imine **31** came from the following experiments. First, a time course of the

Scheme 5. Proposed Mechanism for the Oxidation of Dibenzodiazepine to Phenazine



reaction, performed at 40 °C, was obtained in the first few hours. After 30 min, the GC−MS of the reaction showed the molecular ion peak of imine **31** (see the Supporting Information). Second, *N,N*-dimethyldibenzodiazepine **18**[4] did not form compound **30**, which revealed that the oxidation at the benzylic position could not form an imine. Finally, the formation of dibenzodiazepinone **35** was not observed. Also, dibenzodiaepinone **35**[19] was converted to phenazine **22** in low yield (22%, eq 1). These experiments suggest that the reaction may proceed through the imine **31** excluding the formation of **35**.



The formation of a product other than phenazine **22** was observed after 2 h (see FT-IR study in the Supporting Information), which was characterized as the acid **37** by HRMS data. Attempted conversion of **37** to phenazine under the optimized condition was not successful. Therefore, **37** was obtained only after workup, and the formation of **37** as intermediate in the reaction is unlikely. In a crossover experiment involving two substrates **9** and **15** carried out under the optimized conditions, the formation of only two phenazines **21** and **27** was observed; no other product was observed. This experiment suggests that the intramolecular C−N bond formation in aminyl radical (similar to **36**) occurs more rapidly than the intermolecular C−N bond formation. The C−N bond formation would be energetically favorable than abstraction of H• from the solvent.[18c]

Finally, the oxidation of **10** to **22** in the presence of a radical scavenger was not successful. This fact supports that a free-radical mechanism is likely be operative in this reaction.

In summary, a synthetically useful application of secondary benzylamine oxidation is demonstrated in the tandem oxidative conversion of 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepines to phenazines, which proceeds through C−C and C−N bond cleavage followed by a new C−N bond formation. More applications of

dx.doi.org/10.1021/ol501766m | *Org. Lett.* XXXX, XXX, XXX−XXX

this novel protocol and study of a detailed mechanism are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jlaha@niper.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We greatly appreciate financial support from the CSIR, New Delhi. K.S.S.T. and A.G. thank the CSIR, New Delhi, for the award of Senior Research and Research Associate fellowships, respectively. J.K.L. thanks Prof. Satinder V. Kessar, Panjab University, for insightful discussions.

■ REFERENCES

(1) For review, see: (a) Wang, T.; Jiao, N. *Acc. Chem. Res.* **2014**, *47*, 1137−1145. For some recent reports on C−C bond cleavage, see: (b) Qin, C.; Zhou, W.; Chen, F.; Ou, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 12595−12599. (c) Cai, S.; Zhao, X.; Wang, X.; Liu, Q.; Li, Z.; Wang, D. Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8050−8053. (d) Liu, H.; Dong, C.; Zhang, Z.; Wu, P.; Jiang, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 12570−12574. (e) Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 4258−4263. (f) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401−10404. (g) Liu, X.; Wang, Z.; Cheng, X.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 14330−14333. (h) Li, W.; Zheng, X.; Li, Z. *Adv. Synth. Catal.* **2013**, *355*, 181−190. (i) Sun, H.; Yang, C.; Gao, F.; Li, Z.; Xia, W. *Org. Lett.* **2013**, *15*, 624−627. (j) More, N. Y.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 804−807. (k) Tang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 6528−6532. (l) Lewis, C. A.; Wolfenden, R. *J. Am. Chem. Soc.* **2014**, *136*, 130−136. (m) Sun, J.; Tan, Q.; Yang, W.; Liu, B.; Xu, B. *Adv. Synth. Catal.* **2014**, *356*, 388−394. (n) Maji, A.; Rana, S.; Akanksha; Maiti, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 2428−2432.

(2) For some recent reports on C−N bond cleavage, see: (a) Ueno, S.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 6098−6099. (b) Liu, C.-R.; Li, M.-B.; Cheng, D.-J.; Yang, C.-F.; Tian, S.-K. *Org. Lett.* **2009**, *11*, 2543−2545. (c) Sabiah, S.; Lee, C.-S.; Hwang, W-.S.; Lin, I. J. B. *Organometallics* **2010**, *29*, 290−293. (d) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. *Org. Lett.* **2011**, *13*, 6308−6311. (e) Liu, C.-R.; Wang, T.-T.; Qi, Q-.B.; Tian, S.-K. *Chem. Commun.* **2012**, *48*, 10913−10915. (f) Wang, Y.; Chi, Y.; Zhang, W.-X.; Xi, Z. *J. Am. Chem. Soc.* **2012**, *134*, 2926−2929. (g) Liang, D.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2013**, *15*, 3476−3479. (h) Huang, H.; Ji, X.; Wu, W.; Huang, L.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3774−3782. (i) Zhang, J.; Jiang, J.; Li, Y.; Wan, X. *J. Org. Chem.* **2013**, *78*, 11366−11372. (j) Zhang, X.; Yang, W.; Wang, L. *Org. Biomol. Chem.* **2013**, *11*, 3649−3654. (k) Abe, M.; Watanabe, S.; Tamura, H.; Boinapally, S.; Kanahara, K.; Fujiwara, Y. *J. Org. Chem.* **2013**, *78*, 1940−1948. (l) Sharma, S.; Han, S.; Kim, M.; Mishra, N. K.; Park, J.; Shin, Y.; Ha, J.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2014**, *12*, 1703−1706. (m) Tobisu, M.; Nakamura, K.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 5587−5590.

(3) For some recent reports on both C−C and C−N bond cleavage, see: (a) Feng, P.; Sun, X.; Su, Y.; Li, X.; Zhang, L.-H.; Shi, X.; Jiao, N. *Org. Lett.* **2014**, *16*, 3388−3391. (b) Li, C.; Zhang, W.-T.; Wang, X.-S. *J. Org. Chem.* **2014**, *79*, 5847−5851.

(4) Laha, J. K.; Tummalapalli, K. S. S.; Gupta, A. *Eur. J. Org. Chem.* **2014**, *37*, 4773−4779.

(5) (a) Sasakura, K.; Sugasawa, T. *Heterocycles* **1981**, *15*, 421−425. (b) Majer, P.; Slaninova, J.; Lebl, M. *Int. J. Peptide Protein Res.* **1994**, *43*, 62−68. (c) Jiu, J.; Mizuba, S.; Hribar, J. *Appl. Environ. Microbiol.* **1977**, *33*, 26−30.

(6) (a) Yamazaki, S. *Chem. Lett.* **1992**, 823−826. (b) Hu, Z.; Kerton, F. M. *Org. Biomol. Chem.* **2012**, *10*, 1618−1624. (c) Zhang, E.; Tian, H.; Xu, S.; Yu, X.; Xu, Q. *Org. Lett.* **2013**, *15*, 2704−2707.

(7) Wu, X. F.; Bheeter, C. B.; Neumann, H.; Dixneuf, P. H.; Beller, M. *Chem. Commun.* **2012**, *48*, 12237−12239.

(8) (a) Goti, A.; Cardona, F.; Soldaini, G. *Org. Synth.* **2005**, *81*, 204. (b) Gella, C.; Ferrer, E.; Alibes, R.; Busque, F.; March, P. D.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6365−6367.

(9) Dols, P. P. M. A.; Folmer, B. J. B.; Hermkens,P.H. H.; Lucas, H.; Ma Rewinkel, J. B. WO 2003084963, 16 October 2003.

(10) Laha, J. K.; Tummalapalli, K. S. S.; Gupta, A. *Eur. J. Org. Chem.* **2013**, *36*, 8330−8335.

(11) (a) Yang, Z.; Chen, X.; Wang, S.; Liu, J.; Xie, K.; Wang, A.; Tan, Z. *J. Org. Chem.* **2012**, *77*, 7086−7091. (b) Yang, Z.; Wang, A.; Chen, X.; Gui, Q.; Liu, J.; Tan, Z.; Wang, H.; Shi, J.-W. *Synlett.* **2013**, *24*, 1549−1554.

(12) (a) Yan, J.; Travis, B. R.; Borhan, B. *J. Org. Chem.* **2004**, *69*, 9299−9302. (b) Moriyama, K.; Takemura, M.; Togo, H. *Org. Lett.* **2012**, *14*, 2414−2417.

(13) Qiu, J.; Zhang, R. *Org. Biomol. Chem.* **2013**, *11*, 6008−6012.

(14) Chianese, A. R.; Zeglis, B. M.; Crabtree, R. H. *Chem. Commun.* **2004**, 2176−2177.

(15) (a) Huyser, E. S.; Rose, L. G. *J. Org. Chem.* **1972**, *37*, 851−853. (b) Ogawa, K.; Nomura, Y.; Takeuchi, Y.; Tomoda, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 3031−3035.

(16) (a) Black, D.; Rothnie, N. E. *Aust. J. Chem.* **1983**, *36*, 1149−1157. For imine formation with a related dibenzodiazepine, see: (b) Ishizumi, K.; Mori, K.; Inaba, S.; Yamamoto, H. *Chem. Pharm. Bull.* **1975**, *23*, 2169−2173.

(17) Addition of H_2SO_4 to the imine **31** was suggested by one of the reviewers.

(18) For $K_2S_2O_8$-mediated decarboxylation, see: Brown, P. M.; Dewar, P. S.; Forrester, A. R.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2842−2846. (b) Tanner, D. D.; Osman, S. A. A. *J. Org. Chem.* **1987**, *52*, 4689−4693. (c) Seo, S.; Slater, M.; Greaney, M. F. *Org. Lett.* **2012**, *14*, 2650−2653.

(19) See the Supporting Information for the preparation of compound **35**.