ORGANIC LETTERS

2009
Vol. 11, No. 6
1225−1228

Gold or No Gold: One-Pot Synthesis of Tetrahydrobenz[*b*]azepin-4-ones from Tertiary *N*-(But-3-ynyl)anilines

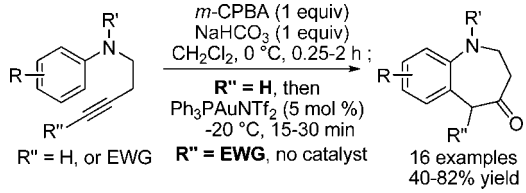
Li Cui, Guozhu Zhang, Yu Peng, and Liming Zhang*

Department of Chemistry, University of Nevada, Reno, Nevada 89557

lzhang@unr.edu

Received January 7, 2009

ABSTRACT



Depending on the tertiary aniline substrates, an efficient, one-pot synthesis of tetrahydrobenz[*b*]azepin-4-ones needs either gold catalysts or no catalyst at all. In the reaction, the aniline nitrogen plays a unique role in relaying "O" from *m*-CPBA to a tethered C−C triple bond, which is inert to the oxidant under the mild reaction conditions.

Tetrahydrobenz[*b*]azepin-4-one is a biologically significant class of benzene-fused heterocycles and has been studied as a mitochondrial benzodiazepine receptor (MBR) antagonist,[1] as an AMPA receptor antagonist,[2] and as oxytocin and vasopressin antagonists (**1**).[3] Oxcarbazepine (**2**), a member of dibenz[*b,f*]azepine drugs including carbamazepine, trimipramine, and imipramine, contains a benz[*b*]azepin-4-one moiety and is used to treat epilepsy and bipolar disorder. Moreover, this structural motif is found in homocryptolepinone (**3**),[4] a natural product isolated from the indigenous Ghanaian medicinal plant *Cryptolepis sanguinolenta*.

While various approaches have been developed to prepare dibenz[*b,f*]azepines including anionic cyclizations,[5] intramolecular Buchwald−Hartwig C−N cross-couplings,[6] and Friedel−Crafts cyclizations,[7] synthetic approaches toward tetrahydrobenz[*b*]azepin-4-ones are limited. Intermolecular 1,3-dipolar cycloaddition between *C*,*N*-diphenylnitrone and allenes followed by in situ rearrangement offers rapid access to these structures but suffers from limited scope, rather rigid

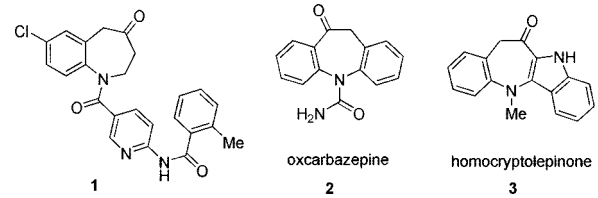


Figure 1. Compounds containing benz[*b*]azepin-4-one motif.

(1) Seko, T.; Katsumata, S.; Kato, M.; Manako, J.-i.; Ohmoto, K. (Ono Pharmaceutical Co., Ltd. , Japan). Application: WO, 2003, 222 pp.

(2) Waetjen, F.; Dahl, B. H.; Drejer, J.; Jensen, L. H. (NeuroSearch A/S, Den.). Application: US, 1995, 8 pp Cont-in-part of US 5,242,918.

(3) Ogawa, H.; Kondo, K.; Yamashita, H.; Kan, K.; Tominaga, M.; Yabuuchi, Y. (Otsuka Pharmaceutical Co., Ltd., Japan). Application: WO, 1994, 159 pp.

(4) Sharaf, M. H. M.; Schiff, P. L., Jr.; Tackie, A. N.; Phoebe, C. H., Jr.; Davis, A. O.; Andrews, C. W.; Crouch, R. C.; Martin, G. E. *J. Hetereocycl. Chem.* **1995**, *32*, 1631–6.

(5) For selected examples, see: (a) MacNeil, S. L.; Gray, M.; Briggs, L. E.; Li, J. J.; Snieckus, V. *Synlett* **1998**, 419–421. (b) Lohse, O.; Beutler, U.; Funfschilling, P.; Furet, P.; France, J.; Kaufmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385–389.

(6) (a) Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2005**, *7*, 4787–4789. (b) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Tetrahedron* **2006**, *63*, 690–702.

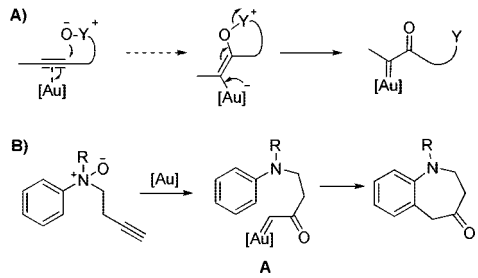
(7) (a) Fuenfschilling, P. C.; Zaugg, W.; Beutler, U.; Kaufmann, D.; Lohse, O.; Mutz, J.-P.; Onken, U.; Reber, J.-L.; Shenton, D. *Org. Process Res. Dev.* **2005**, *9*, 272–277. (b) Kaufmann, D.; Fuenfschilling, P. C.; Beutler, U.; Hoehn, P.; Lohse, O.; Zaugg, W. *Tetrahedron Lett.* **2004**, *45*, 5275–5278.

10.1021/ol900027h CCC: $40.75
Published on Web 02/16/2009

product substitution patterns, and low yields.[8] Other less studied approaches include intramolecular anionic cyclization of *N*-aryl *β*-lactams[9] and ring expansion via the Schmidt reaction.[10] In our opinion, there is still a need for methods that offer synthetic flexibility and efficiency and proceed under mild reaction conditions.

Recent rapid developments in gold catalysis[11] have revealed many fascinating facets of gold chemistry. Among them is the intramolecular oxidation of gold-activated alkynes into α-oxogold carbenes (Scheme 1A). We and others have

Scheme 1. Intramolecular Oxidation of Au-Activated Alkynes: Concept and Design



employed this concept in developing efficient synthetic methods. For example, tetrahydrobenzothiepinones[12,13] can be readily prepared using appropriately tethered sulfoxide as the oxidant, and nitrones were used as internal oxidant to generate azomethine ylides for subsequent cycloadditions.[14]

We surmised that a tethered amine oxide should work similarly as an internal oxidant and lead to the generation of α-oxo gold carbene **A**, which could cyclize to the benzene ring and thus offer an expedient synthesis of tetrahydrobenz-[*b*]azepin-4-ones (Scheme 1B). Herein, we report the implementation of this design with terminal alkyne substrates in an Au-catalyzed one-pot reaction. Surprisingly, for substrates with an electron-withdrawing group (EWG) at the alkyne terminus, tetrahydrobenz[*b*]azepin-4-ones were formed directly *without any gold catalyst*!

At the onset, *N*-(but-3-ynyl)-*N*-methylaniline was treated with *m*-CPBA (*m*-chloroperbenzoic acid) to generate the corresponding *N*-oxide, which was not stable in its nonprotonated form.[15] Consequently, it was isolated as its hydrochloric salt and characterized. Treatment of the hydrochloric salt with $Ph_3PAuNTf_2$[16] (5 mol %), to our delight, indeed gave the expected tetrahydrobenz[*b*]azepin-4-one **5** albeit in only 30% yield. We reasoned that the *N*-oxide could be used to study the reaction conditions without isolation. As shown in Table 1, the desired reaction indeed occurred smoothly, and azepinone **5** was formed in good overall yields with various gold(I) and gold(III) catalysts (entries 1−5). Noticeably, $AgBF_4$ also catalyzed this reaction (entry 6) albeit with less efficiency, and $HNTf_2$ (1 equiv) did not catalyze the formation of **5** at all (entry 7). Not much reaction occurred using $PtCl_2$ as catalyst (entry 8) likely due to the low reaction temperature, as usually heating is required for $PtCl_2$/toluene catalytic systems. Further optimization of the reaction conditions with stable and affordable $Ph_3PAuNTf_2$ revealed that this reaction performed better at a lower temperature in the presence of $NaHCO_3$ (1 equiv, entry 9), and compound **5** was isolated in 79% yield.

This two-step, one-pot efficient formation of the azepin-4-one ring is remarkable considering general difficulties in constructing seven-membered rings. Moreover, the aniline nitrogen in **4** plays an interesting role of relaying "O" from *m*-CPBA to the gold-activated C−C triple bond, which is particularly noteworthy considering that alkynes are generally inert to *m*-CPBA oxidation under the reaction conditions (i.e., 0 °C in CH_2Cl_2).[17] Additionally, the reaction conditions were mild, and the aniline substrate can be easily prepared.

The scope of this chemistry was probed first by varying substitutions on the benzene ring. As shown in Table 2, substituents with different electronic characters were tolerated in the meta and para positions (entries 1−8), and electron-donating groups such as MeO (entry 3) and Me (entries 5 and 7) as well as weakly electron-withdrawing groups such as halides (entries 1 and 2) led to better yields than those of strongly electron-withdrawing (entries 4 and 6). In most cases, acceptable to good yields were obtained in this two-step, one-pot transformation. In the case of substrates with meta substituents (entries 4, 5, and 8), the regioselectivity is low; moreover, in the case of *m*-NO_2, the major product was surprisingly the more hindered ortho-substitution isomer. Noticeably, functional groups such as halides and NO_2 on the benzene ring allow easy derivatization of these bicyclic heterocycles. In addition, a benzyl group was suitable as the aniline nitrogen substituent (entry 9), and its ready removal would open a venue to functionalize the azepinone nitrogen.

(8) (a) Blechert, S. *Liebigs Annal.Chem.* **1985**, 673–82. (b) Padwa, A.; Kline, D. N.; Norman, B. H. *J. Org. Chem.* **1989**, *54*, 810–17. (c) Tufariello, J. J.; Ali, S. A.; Klingele, H. O. *J. Org. Chem.* **1979**, *44*, 4213–15.

(9) Verboom, W.; Berga, H. J.; Trompenaars, W. P.; Reinhoudt, D. N. *Tetrahedron Lett.* **1985**, *26*, 685–8.

(10) James, R. A.; Kohn, C. A.; Rees, A. H.; Verschuren, R. E. *J. Heterocycl. Chem.* **1989**, *26*, 793–5.

(11) For selected reviews on gold catalysis, see: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (e) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917–4938. (f) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (g) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (h) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (i) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.

(12) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161.

(13) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156–5159.

(14) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040–7043.

(15) Washing the reaction mixture with aqueous Na_2CO_3 (5%) led to mostly decomposition of the *N*-oxide, and no cyclized product **5** was detected. Surprisingly, a small amount of aniline **4** was observed although the initial *m*-CPBA oxidation was complete.

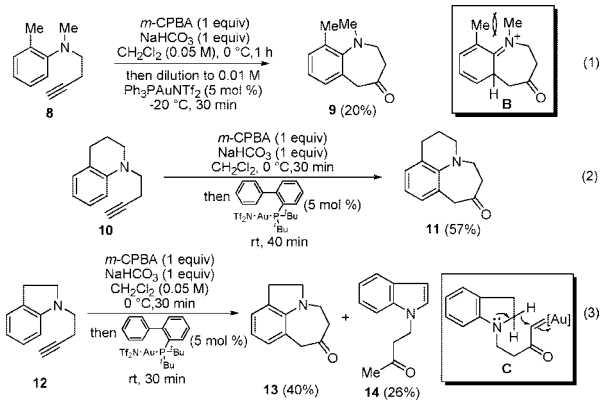
(16) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

(17) (a) Mandal, S. K.; Roy, S. C. *Tetrahedron* **2007**, *63*, 11341–11348. (b) Zinzalla, G.; Milroy, L.-G.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 1977–2002.

(18) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488–16489.

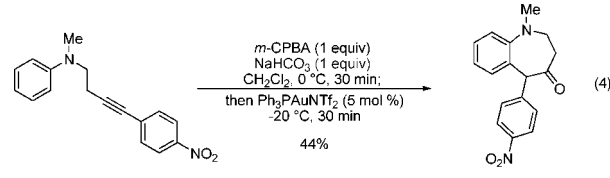
(19) For examples of alkyne oxidations using other oxidants, see: (a) Curci, R.; Fiorentino, M.; Fusco, C.; Mello, R.; Ballistreri, F. P.; Failla, S.; Tomaselli, G. A. *Tetrahedron Lett.* **1992**, *33*, 7929–32. (b) Ishii, Y.; Sakata, Y. *J. Org. Chem.* **1990**, *55*, 5545–7.

The aniline substrate with an *o*-Br underwent *m*-CPBA oxidation sluggishly, presumably due to steric hindrance, and subsequent Au catalysis with partial *N*-oxide formation led to little benz[*b*]azepinone formation. In the case of *o*-Me (i.e., compound **8**), the oxidation proceeded to completion in 1 h, but one-pot gold catalysis gave the desired product **9** in only 20% yield (eq 1). This low efficiency is likely due to the severe $A^{1,3}$ strains experienced by the iminium resonance structure (i.e., **B**) of the likely *σ*-complex intermediate during cyclization.



We anticipated that ortho-substitutions can be accommodated in bicyclic systems. For example, 1,2,3,4-tetrahydroquinoline substrate **10** underwent the reaction under optimized reaction conditions, affording tricyclic azepin-4-one **11** in a serviceable yield (eq 2). In the case of 2,3-indoline substrate **12**, the desired product **13** was formed in 40% yield (eq 3). Much to our surprise is the formation of indole **14**. The simultaneous aromatization and methyl ketone formation suggests that a hydride migration to the Au carbene (as shown in intermediate **C**),[18] followed by aromatization and protodeauration.

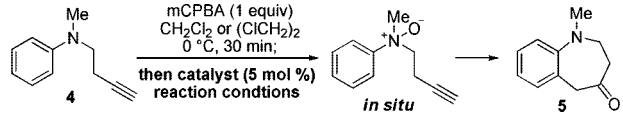
Next, we studied the reaction scope by varying the alkyne chain. While longer alkyne chains such as pent-4-ynyl did not yield benzene-fused larger heterocycles, substitutions such as ^{i}Pr or phenyl at the but-3-ynyl group α to the nitrogen adversely affected the *N*-oxide formation, and subsequent Au catalysis could not be studied. Substitutions at the butyne terminus were then studied. A phenyl group did not lead to any desired product, but a more electron-deficient *p*-NO_2Ph group underwent the reaction in a fair yield (eq 4). We reason that other EWGs at the alkyne terminus should equally, if not better, facilitate the azepin-4-one formation. Our prediction was indeed correct but not without surprise! When a methoxycarbonyl group was used, tetrahydrobenz[*b*]azepin-4-one **16a** was formed *without the addition of any gold catalyst*; moreover, the reaction was rather efficient (73% yield). Substrates with other electron-withdrawing groups including acetyl (**15b**), benzoyl (**15c**), and methanesulfonyl (**15d**) groups all underwent this uncatalyzed reaction smoothly, yielding tetrahydrobenz[*b*]azepin-4-ones with the EWG at the 5 position in fair to good yields.



15 (EWG)	reaction conditions	**16** (yield)
15a (MeO_2C)	0 °C, 30 min	**16a** (73%)
15b (Ac)	0 °C, 30 min	**16b** (76%
15c (Bz)	0 °C, 30 min	**16c** (82%)
15d (Ms)	-20 °C, 4 h	**16d** (63%)

A mechanism similar to the gold-catalyzed reactions is envisioned (Scheme 2): the aniline is first oxidized by *m*-CPBA to the corresponding *N*-oxide; then, carbene **D** is formed via an intramolecular oxidation of the electron-deficient alkyne by the aniline *N*-oxide; the EWG in this

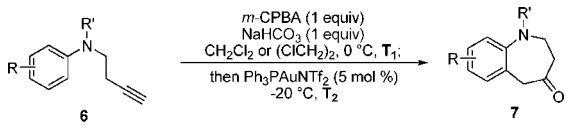
Table 1. Screening Reaction Conditions

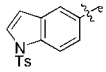


entry[a]	catalyst	reaction conditions	yield[b,c] (%)
1	$Ph_3PAuNTf_2$	$(ClCH_2)_2$, 0 °C, 30 min	76
2	dichloro(2-picolinato)gold (III)	$(ClCH_2)_2$, 0 °C, 30 min	70
3	(2-biphenyl)$^{t}Bu_2PAuNTf_2$	$(ClCH_2)_2$, 0 °C, 3 h	65
4	$(p\text{-}CF_3Ph)_3PAuNTf_2$	$(ClCH_2)_2$, 0 °C, 30 min	66
5	$Ph_3PAuCl/AgSbF_6$	$(ClCH_2)_2$, 0 °C, 30 min	55
6	$AgBF_4$	$(ClCH_2)_2$, 0 °C, 30 min	38
7	$HNTf_2$ (1 equiv)	$(ClCH_2)_2$, 0 °C, 1 h	0[d]
8	$PtCl_2$	$(ClCH_2)_2$, 0 °C, 1 h	5[e]
9	**$Ph_3PAuNTf_2$**	**CH_2Cl_2, $NaHCO_3$ (1 equiv), −20 °C, 30 min**	**84**(79[f])

[a] The reactions were performed in one-pot in round-bottom flasks, and the substrate concentrations were 0.05 M. [b] NMR yield using diethyl phthalate as the internal reference. [c] Complete conversion. [d] Most of the *N*-oxide intermediate remains. [e] 65% of the *N*-oxide left. [f] Isolated yields.

Table 2. Scope Studies with Variously Aryl-Substituted *tert*-Anilines

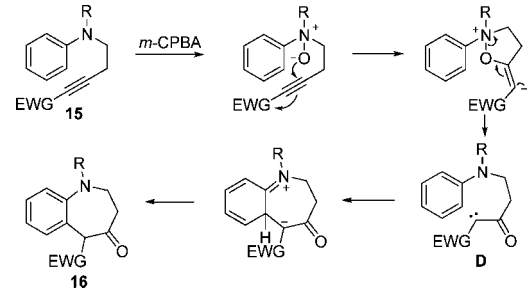


entry[a]	6	R	R'	T_1/T_2	7	yield (%)[b]
1	**6a**	*p*-Br	Me	30 min/30 min	**7a**	73
2	**6b**	*p*-I	Me	30 min/30 min	**7b**	68
3	**6c**	*p*-MeO	Me	15 min/15 min	**7c**	73
4	**6d**	*m*-NO_2	Me	2 h/30 min	**7d**	58[c]
5	**6e**	*m*-Me	Me	30 min/30 min	**7e**	70[d]
6	**6f**	*p*-EtO_2C	Me	30 min/30 min	**7f**	40
7	**6g**	*p*-Me	Me	30 min/30 min	**7g**	70
8	**6h**		Me	30 min/30 min	**7h**	65[f]
9	**6i**	H	Bn	2 h/30 min	**7i**	68

[a] The substrate concentration was 0.05 M. [b] Isolated yield. [c] Para/ortho = 1:1.35. [d] Para/ortho = 1:1. [e] This is the R-Ph instead of just R group. [f] Para/ortho = 1:1.

oxidation facilitates the initial nucleophilic 5-*exo*-*dig* cyclization, similar to the activation role of gold complexes in the case of terminal alkyne substrates; subsequent cyclization to the benzene ring affords azepinone **16**. Direct oxidation of the C−C triple bond to generate carbene **D** via an oxirene intermediate is highly unlikely considering its electron-deficient nature and the inert nature of normal alkynes toward *m*-CPBA oxidation at 0 °C.[15,19] These uncatalyzed reactions revealed again the unique role of the aniline nitrogen in relaying "oxygen" from *m*-CPBA to the C−C triple bond inert to the oxidant under the reaction conditions (i.e., 0 °C, CH_2Cl_2).

Scheme 2. Proposed Mechanism for the Uncatalyzed Reaction



In summary, an efficient, one-pot synthesis of tetrahydrobenz[*b*]azepin-4-ones is developed. The ready access to tertiary aniline substrates and the mild reaction conditions should enhance its synthetic potential. For aniline substrates with tethered terminal alkynes, this reaction requires gold catalysis; for those substrates with EWGs at the alkyne terminus, the reaction proceeds without the addition of any gold catalyst. In either case, the aniline nitrogen plays a unique role in relaying "O" from *m*-CPBA to the tethered C−C triple bond, which is inert to the oxidant under the mild reaction conditions.

Acknowledgment. We thank NSF CAREER (CHE-0748484) and Amgen for generous financial support. The NMR spectrometers are funded by NSF CHE-0521191.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900027H