Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 3811–3814
Tetrahedron Letters

A regioselective synthesis of 3-benzazepinones via intramolecular hydroamidation of acetylenes

Ying Yu, Gregory A. Stephenson and David Mitchell*

Chemical Product R&D, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

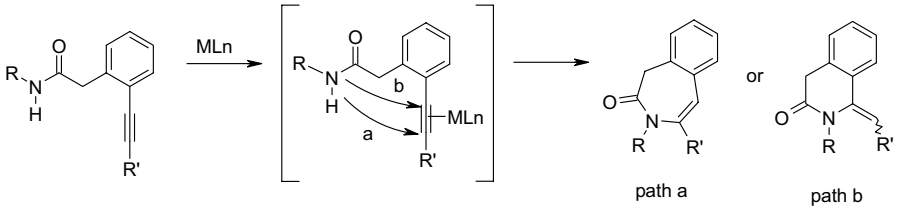
Received 8 February 2006; revised 30 March 2006; accepted 31 March 2006
Available online 27 April 2006

Abstract—Synthesis of 3-benzazepinones by palladium-catalyzed intramolecular addition of amides to alkynes is achieved. Phenyl acetylenes substituted in the *ortho*-position with tethered amide functionality were prepared in a few steps from readily available starting materials. It was found that 5% $Pd(OAc)_2(PPh_3)_2$ and KOH most effectively promoted cyclization. When the tethered group is an acetamide and an alkyl substituent is on the acetylene unit, regioselective 3-benzazepinone synthesis could be achieved in good yields.

The benzazepine framework is frequently found in important pharmaceuticals. In particular, the 3-benzazepines exhibit biological activities related to their more popular benzodiazepines.[1] Each molecule presents unique challenges for the seven-membered nitrogen heterocyclic ring formation, especially in large scales. For example, a common approach centers on lactam formation using ammonium salts or Friedel–Crafts alkylation.[2] However, during our course of study, a large excess of strong acids or Lewis acids was required for the cyclization, which led to problematic workup and hazardous waste generation.

Our investigation of 3-benzazepinone synthesis involved a metal catalyzed amide heteroannulation reaction of acetylene for the ring construction. This strategy for intramolecular nitrogen heterocyclic ring formation is common for both five- and six-membered ring formation such as pyrroles, indoles and isoindoles;[3] however, few applications have been reported on synthesizing seven-membered ring analogs.[4] We were also interested in the potential regioselectivity of such a transformation by examining catalyst and reaction conditions. As depicted in Scheme 1, an *endo* addition of amide to alkyne would provide benzazepinone (path a). An *exo* addition (path b) would lead to isoquinolinone. Herein, we report the development and general synthesis of 3-benzazepinone via palladium catalyzed addition of tethered amides to phenyl acetylenes.

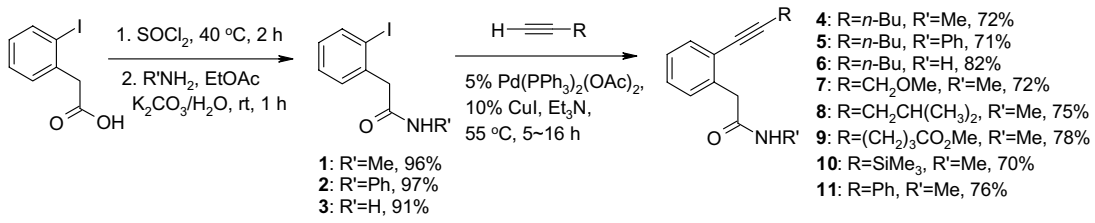
The requisite 2-alkynyl benzeneacetamides were obtained by amidation of commercially available 2-iodo phenylacetic acid followed by Sonogashira coupling[5] with terminal alkynes. As shown in Scheme 2, benzeneacetamides with different alkynyl and *N*-substitutions were obtained in good yields after a single crystallization.



Scheme 1. *endo* and *exo* hydroamidation of alkynes.

* Corresponding author. Tel.: +1 317 276 1384; fax: +1 317 276 4507; e-mail: dmit@lilly.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.198



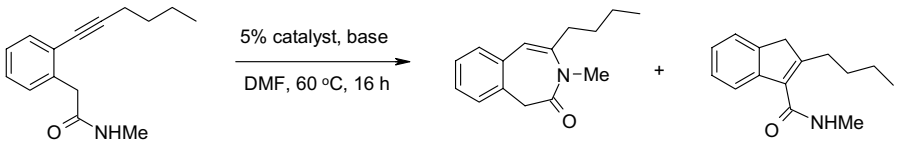
Scheme 2. Synthesis of *o*-alkynyl benzeneacetamides.

In pursuing the desired nucleophilic addition of amide to the triple bond in *o*-alkynyl benzeneacetamides, we reasoned that the activation of both the triple bond and the amide proton might be essential. Exploration of benzazepinone formation was probed by heating *o*-(1-hexynyl)-*N*-methyl benzeneacetamide (**4**), a base and a metal additive in DMF for 16 h. As shown in Table 1, bases such as Et_3N, Cs_2CO_3, and $LiN(TMS)_2$[6] failed to provide any desired product (entries 1–3). Alternate basic conditions involving NaOH or KOH afforded the desired seven-membered ring compound 1,3-dihydro-3-methyl-4-butyl-2*H*-3-benzazepin-2-one **12** in low yields (entries 4–6). An indene compound **13** was identified as a byproduct, generated from the nucleophilic addition of the benzylic CH_2 to the triple bond followed by isomerization.[7] In the case of KO(*t*-Bu) as base, the yield of **13** was comparable with benzazepinone **12** (entry 6). Metal additives $Cu(OTf)_2$, AgOTf and $ZnCl_2$ were applied thereafter along with KOH for the activation of the triple bond as Lewis acids.[8] However, **12** was still obtained in <40% yield (entries 7–9). Fortunately, the yield of **12** was improved to >80% with ~5% byproduct **13** in the presence of KOH or NaOEt and 5% $Pd(OAc)_2(PPh_3)_2$ (entries 10–11). The above observations indicated that hydroamidation of acetylene could be achieved by using strong bases which would directly deprotonate the amide proton;[9] however, high basicity would also lead to fast deprotonation of the benzylic position and formation of five-membered ring indene byproduct in moderate yields. A Pd catalyst would facilitate the hydroamidation process;[10] therefore, a weaker base could be utilized and the formation of indene byproduct was minimized.

Further optimization of the reaction conditions showed that $Pd(PPh_3)_2(OAc)_2$, $Pd(PPh_3)_2Cl_2$, and $Pd(PhCN)_2Cl_2$ were superior than $Pd(OAc)_2$. Although both Pd(II) and Pd(0) have been reported as efficient in catalyzing hydroamidation/amination of acetylenes, in our cases Pd_2dba_3 was not effective.[11] The optimal condition was found to be DMF or DMA as solvent at 50–60 °C. Solvents such as THF, DMSO, acetonitrile and toluene resulted in lower yields. Benzazepinone **12** was obtained as a white crystalline solid and its ^1H NMR spectrum exhibited certain unique characters: a singlet for the olefin proton (H-5) at 6.5 ppm and two broad peaks for the benzylic CH_2.[12] Interestingly, hydroamidation of the triple bond occurred exclusively at the *endo* position in the cyclization of benzeneacetamide **4** and no *6-exo* product was observed.

The methodology has been successfully applied in synthesizing various 4-alkyl-2*H*-3-benzazepin-2-one compounds. As illustrated in Table 2, benzazepinones with

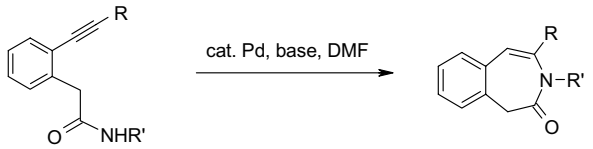
Table 1. Formation of benzazepinone **12** from benzeneacetamide **4**



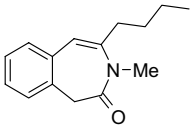
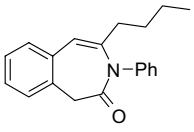
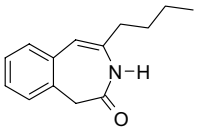
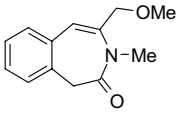
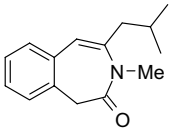
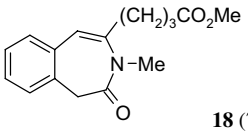
Entry	Catalyst	Base (equiv)	Recovered **4**[a] (%)	**12**[a] (%)	**13**[a] (%)
1	None	Et_3N (2)	100	0	0
2	None	Cs_2CO_3 (2)	100	0	0
3	None	$LiN(TMS)_2$ (1)	Trace[b]	0	0
4	None	NaOH (2)	75	20	Trace
5	None	KOH (2)	62	35	Trace
6	None	KO(*t*-Bu) (1)	0	55	45
7	$Cu(OTf)_2$	KOH (2)	58	34	4
8	AgOTf	KOH (2)	64	30	Trace
9	$ZnCl_2$	KOH (2)	57	38	0
10	$Pd(PPh_3)_2(OAc)_2$	KOH (2)	Trace	82[c]	6
11	$Pd(PPh_3)_2(OAc)_2$	NaOEt (2)	0[b]	80[c]	5

[a] LC/MS yield.
[b] Decomposition observed.
[c] Isolated yield.

Table 2. Synthesis of 4-alkyl-2*H*-3-benzazepin-2-ones from *o*-alkynyl benzeneacetamides

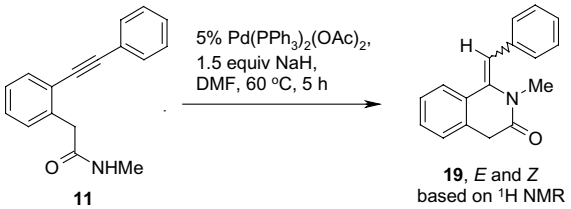


4-10

Entry	Benzeneacetamide	Conditions	3-Benzazepin-2-one (isolated yield)
1	**4**	5% $Pd(OAc)_2(PPh_3)_2$, 2 equiv KOH, DMF, 60 °C, 16 h	 **12** (82%)
2	**5**	5% $Pd(OAc)_2(PPh_3)_2$, 2 equiv KOH, DMF, 50 °C, 48 h	 **14** (61%)
3	**6**	5% $Pd(PhCN)_2Cl_2$, 2 equiv NaH, DMF, 80 °C, 18 h	 **15** (55%)
4	**7**	5% $Pd(OAc)_2(PPh_3)_2$, 1.2 equiv KOH, DMF, 55 °C, 15 h	 **16** (42%)
5	**8**	5% $Pd(OAc)_2(PPh_3)_2$, 3 equiv KOH, DMF, 60 °C, 16 h	 **17** (80%)
6	**9**	5% $Pd(OAc)_2(PPh_3)_2$, 2 equiv NaOEt, DMF, 50 °C, 16 h; then MeI, K_2CO_3, rt, 2 h	 **18** (71%)
7	**10**	5% $Pd(OAc)_2(PPh_3)_2$, 2 equiv KOH, DMF, 50 °C, 4 h	— (Decomposition)

N-methyl, *N*-phenyl, and *N*-hydrogen substitutions could all be synthesized in good yields. It is noted that lower yields were obtained with *N*-Ph and *N*-H substitutions (entries 2–3) due to weaker nucleophilicity of amide substrates, and neither high temperature nor strong basicity could improve the yields. Moderate yield of **16** was obtained due to elimination of methyl propargyl ether substrate in compound **7** (entry 4). Unfortunately, cyclization of TMS-ethynyl benzeneacetamide **10** under the same condition was not successful and only decomposition products were observed (entry 7).[13]

On the other hand, heating phenylethynyl benzeneacetamide **11** with 1.5 equiv NaH and 5% $Pd(PPh_3)_2(OAc)_2$ in DMF at 60 °C gave *6-exo* cyclization product 3-isoquinolinone derivative.[14] ^{1}H NMR spectrum indicated that the cyclization first yielded **19** as a mixture of *E* and *Z* isomers: singlet of benzylic CH_2 at 3.74 ppm, 6.56 ppm (*Z*-isomer) and 6.41 (*E*-isomer) ppm for olefin H, 2.93 ppm (*Z*-isomer) and 3.38 ppm (*E*-isomer) for *N*-CH_3 substitution (Scheme 3).[15] However, **19** was not stable and converted into multiple compounds upon standing at room temperature.[16] The formation of *6-exo* cyclization product supports the assumption that the



Scheme 3. Formation of isoquinolinone **19**.

cyclization is electronically oriented by the acetylene substrate.[17]

In summary, the synthesis of 3-benzazepinones has been achieved from the palladium-catalyzed intramolecular addition of amides to alkynes. Optimum conditions were developed for the preparation of 3-benzazepinones. It has been found that the regioselective transformation is dependent on the amide, alkyne substitution or reaction conditions. The utilization of this methodology in the synthesis of isoquinolinones and indenes is currently being explored.

Acknowledgments

We would like to thank the LRL Physical Chemistry Department and Dr. Thomas Zennie, for obtaining analytical data. Y.Y. gratefully acknowledges the CPR&D management, for a postdoctoral fellowship in support of this work.

References and notes

1. Nadler, G.; Faivre, J.; Forest, M.; Cheval, B.; Martin, M.; Souchet, M.; Gout, B.; Bril, A. *Bioorg. Med. Chem.* **1998**, *11*, 1993, and the references cited therein.
2. (a) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875; (b) Kawase, M.; Motohashi, N.; Niwa, M.; Nozaki, M. *Heterocycles* **1997**, *45*, 1121; (c) Zhai, H.; Luo, S.; Ye, C.; Ma, Y. *J. Org. Chem.* **2003**, *68*, 8268; (d) Smith, B. M.; Smith, J. M.; Tsai, J. H.; Schultz, J. A.; Gilson, C. A.; Estrada, S. A.; Chen, R. R.; Park, D. M.; Prieto, E. B.; Gallardo, C. S.; Sengupta, D.; Thomsen, W. J.; Saldana, H. R.; Whelan, K. T.; Menzaghi, F.; Webb, R. R.; Beeley, N. R. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1467.
3. For recent reviews, see (a) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42; (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167.
4. Synthesis of 3-benzazepines from propargyl ethers using a Pd catalyst with a bidentate ligand was reported Tsubakiyama, M.; Sato, Y.; Mori, M. *Heterocycles* **2004**, *64*, 27.
5. Sonogashira, K.; Tohda, Y.; Hahihara, N. *Tetrahedron Lett.* **1975**, 4467.
6. (a) Koseki, Y.; Kusano, S.; Nagasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3517; (b) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*, 8855; (c) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885.
7. The structure of compound **13** was confirmed by NOE NMR experiments.
8. (a) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841; (b) Hiroya, K.; Itoh, S.; Sakanoto, T. *J. Org. Chem.* **2004**, *69*, 1126.
9. Amide proton $pK_a = 17$ (March, J. *Advanced Organic Chemistry*, 4th ed; 1992; pp 250–252). A base as strong as NaH could promote direct hydroamidation of alkyne (a) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem., Sect. B: Org. Chem. Incl., Med. Chem.* **1989**, *28B*, 67; (b) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078.
10. For examples of Pd-catalyzed hydroamidation of alkynes, see Ref. 4 and (a) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435; (b) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, *7*, 1145; (c) Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *J. Organomet. Chem.* **2001**, *624*, 244; (d) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 8068.
11. Heating compound **4**, 2 equiv KOH and 2.5% Pd_2dba_3 in DMF at 60 °C for 16 h gave **12** in 32% LC/MS yield. Usage of ligand dppb could improve the yield of **12** to ~60%.
12. General procedure for benzazepinone synthesis: 1.15 g 2-(1-hexynyl)-*N*-methyl benzeneacetamide **4** (5 mmol), 0.19 g $Pd(OAc)_2(PPh_3)_2$ (0.25 mmol) and 0.66 g KOH (10 mmol) were added to a flask and purged with N_2. 25 mL DMF was then added and the mixture was stirred at 50 °C for 16 h. The reaction mixture was concentrated and the residue was partitioned between EtOAc and H_2O. EtOAc layer was washed with brine and dried with $MgSO_4$. The residue after evaporation was subjected to silica gel plug chromatography (hexane–EtOAc = 1:1) to give 1,3-dihydro-3-methyl-4-butyl-2*H*-3-benzazepin-2-one **12** as an off-white solid in 82% yield (0.94 g). Mp 57–58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.34 (m, 4H), 6.5 (s, 1H), 3.65 (br s, 1H), 3.44 (br s, 1H), 3.09 (s, 3H), 2.64 (br s, 1H), 2.44 (br s, 1H), 1.42–1.57 (m, 4H), 0.99 (t, $J = 7.2$, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 142.5, 133.8, 133.2, 128.2, 128.1, 127.0, 126.8, 118.0, 43.0, 35.1, 31.8, 30.5, 22.2, 13.8. IR (KBr, cm^{-1}): 2949, 2926, 2868, 1657, 1419, 1349, 1329, 1078, 931, 849, 765, 582. Anal. Calcd for $C_{15}H_{19}NO$ (MW 229.15): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.49; H, 8.23; N, 6.17. *N*-Methyl 2-butyl-3-indenecarboxamide **13** was isolated as a white solid. Mp 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, $J = 7.8$, 1H), 7.39 (d, $J = 7.2$, 1H), 7.27 (t, $J = 7.5$, 1H), 7.16 (t, $J = 7.5$, 1H), 5.77 (br s, 1H), 3.42 (s, 2H), 3.02 (d, $J = 4.5$, 3H), 2.70 (t, $J = 7.8$, 2H), 1.53–1.63 (m, 2H), 1.38 (sext, $J = 7.5$, 2H), 0.93 (t, $J = 7.5$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 152.5, 143.2, 142.1, 134.5, 126.7, 124.8, 123.8, 120.0, 41.3, 32.1, 29.5, 26.4, 22.9, 14.1. IR (KBr, cm^{-1}): 3289, 2953, 2871, 1639, 1589, 1543, 1406, 1380, 1260, 1155, 945, 756, 709. Anal. Calcd for $C_{15}H_{19}NO$ (MW 229.15): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.61; H, 8.28; N, 6.06.
13. The corresponding desilylated acetylene did not give any benzazepinone product either.
14. It should be noted that heating NaH in DMF should be handled with care because of safety issues. Thanks to a reviewer's suggestion to add this note.
15. The structure was proposed based on the reported data of analogous compounds (Kubo, Y.; Suto, M.; Tojo, S.; Araki, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 771), 1-benzyl-2*H*-isoquinolin-3-one (Cánepa, A. S.; Bravo, R. D. *J. Heterocycl. Chem.* **2004**, *41*, 979) and 3-methyl-4-phenyl-2*H*-3-benzazepin-2-one (Kato, H.; Kobayashi, T.; Horie, K.; Ogura, K.; Moriwaki, M. *J. Chem. Soc., Perkin Trans.* 1 **1993**, 1055).
16. No further purification of the mixture was performed. Possible subsequent reactions with **19** include tautomerization, oxidation, and dimerization.
17. Heating 2-[1-(4-methoxyphenyl)ethynyl]-*N*-methyl benzeneacetamide with NaH in DMF at 60 °C; however, gave *6-exo* cyclization products as well.