
# Efficient one-pot synthesis of 1,3-dihydro-2*H*-pyrrol-2-one derivatives via aza-oxyallylic cations

Gangqiang Wang, Rongxing Chen, Minghu Wu, Shaofa Sun, Xing Luo, Zhi Chen, Haibing Guo, Carlos Chong, Yalan Xing

PII: S0040-4039(17)30070-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.01.048
Reference: TETL 48551

To appear in: *Tetrahedron Letters*

Received Date: 10 November 2016
Revised Date: 5 January 2017
Accepted Date: 13 January 2017

Please cite this article as: Wang, G., Chen, R., Wu, M., Sun, S., Luo, X., Chen, Z., Guo, H., Chong, C., Xing, Y., Efficient one-pot synthesis of 1,3-dihydro-2*H*-pyrrol-2-one derivatives via aza-oxyallylic cations, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.01.048

# Efficient One-pot Synthesis of 1,3-Dihydro-2*H*-pyrrol-2-one Derivatives via Aza-oxyallylic Cations

Gangqiang Wang,[a,] Rongxing Chen,[a] Minghu Wu, Shaofa Sun*[,a] Xing Luo,[a] Zhi Chen,[a] Haibing Guo,[a] Carlos Chong,[b] Yalan Xing,*[,b]

*a)*. School of Nuclear Technology and Chemistry & Biology, Hubei University of Science and Technology, Xianning 437100, China; *b)*. Department of Chemistry, William Paterson University, 300 Pompton Rd, Wayne, NJ 07470, USA

Abstract: An efficient synthesis of functionalized 1,3-dihydro-2*H*-pyrrol-2-one was developed based on a [3+2] cycloaddition reaction of aza-oxyallylic cations and alkynes. With this novel method, a variety of substituted alkynes were readily converted into their corresponding pyrrolidinone analogues at room temperature. The protocol features easy operation, ambient temperature, good yields, readily available starting materials, and broad functional group tolerance.

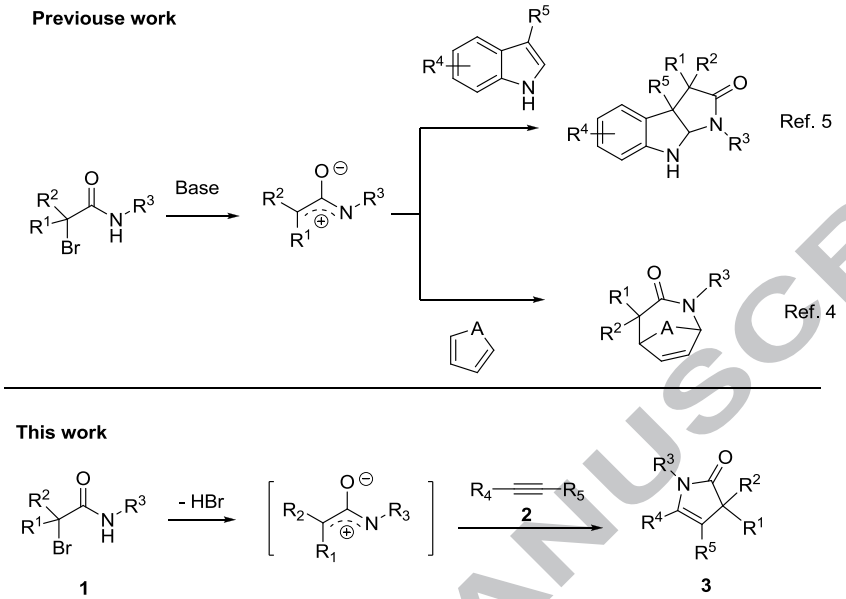
Key word: Aza-oxyallylic Cation; Alkynes; Cycloaddition

**Introduction**

Recently, the aza-oxyallylic cation has emerged into a useful synthetic intermediate for the construction of heterocycles due to its unique chemical features.[1] The existence of the aza-oxyallylic cation was first proposed by Sheehan in 1960s[2] and confirmed by Sakamoto in 1993.[3] However, the first reported application of the aza-oxyallylic cation in organic synthesis was not until 2011 by Jeffrey in his [4+3] cycloaddition reaction of aza-oxyallylic cations with dienes.[4] Later on, Wu group and Liao group utilized [3+2] cycloaddition reactions of aza-oxyallylic cations and alkenes for the synthesis of heterocycles.[5]

As part of our effort to develop efficient methodologies for the synthesis of bio-active heterocyclic compounds, we decided to explore the [3+2] cycloaddition reaction of aza-oxyallylic cations and alkynes to prepare pyrrolidinones structures. To the best of our knowledge, the [3+2] cycloaddition of aza-oxyallylic cations and alkynes has not been reported. Pyrrolidinones are often found in biologically active natural products.[6] They are also valuable starting materials in organic synthesis due to their ability to react as acceptors in conjugate addition reactions of

organocuprates, enolates, and nitrogen nucleophiles.[7] Moreover, Pyrrolidinones are essential key intermediates for the synthesis of pyrrolidines which exhibit very important biological activities.[8]

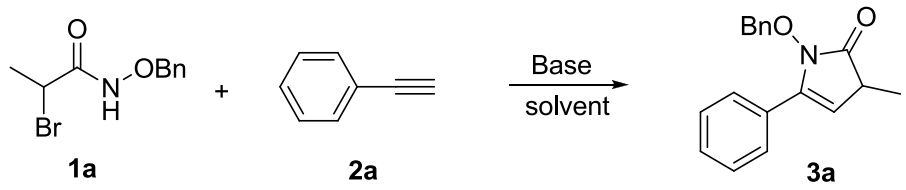



**Scheme 1** Synthesis of 1,3-Dihydro-2*H*-pyrrol-2-ones Derivatives

There are only a few practical synthetic routes for the synthesis of pyrrolidinones available in literature, and the reported syntheses employ harsh reaction conditions such as high temperature and pressure or the use of transition metal catalysts. [9] Herein, we report our studies on the efficient synthesis of 1,3-dihydro-2*H*-pyrrol-2-one derivatives using the cycloaddition of aza-oxyallylic cations and alkynes.

**Results and Discussion**

First, α-haloamide **1a** was chosen as the model substrate to react with phenylacetylene **2a** for the investigation of the optimal reaction conditions. $Na_2CO_3$ served as the base to generate aza-oxyallylic cation from α-haloamide **1a**. Many different solvents such as $CH_3CN$, THF, DCM, DMF, $CH_3OH$, $CF_3CH_2OH$, and Hexafluoroisopropanol (HFIP) (entries 1-7) were tested; HFIP was found to give the best yield of the pyrrolidinone **3a** (90%) and shortest reaction time (10 h). We believe HFIP is a good solvent for this reaction because the aza-oxyallylic cation intermediate is more stable in a strong polar solvent.[4,5] Next, we explored different bases using HFIP as the optimal solvent. Organic bases such pyridine, DBU and TEA (entry 8-10), did not produce the desired product. When inorganic bases such as $K_2CO_3$, NaOAc, and NaOH (entries 11-13) were utilized as bases, desired products were generated in moderate yields.



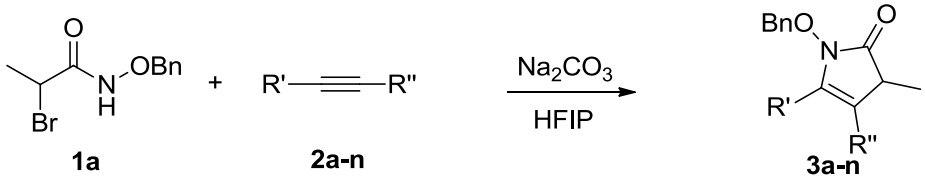

| Entry[a] | Base | Solvent | T | Yield[b] |
|---|---|---|---|---|
| 1 | $Na_2CO_3$ | $CH_3CN$ | 24h | n.r. |
| 2 | $Na_2CO_3$ | THF | 24h | n.r. |
| 3 | $Na_2CO_3$ | $CF_3CH_2OH$ | 24h | n.r. |
| 4 | $Na_2CO_3$ | HFIP | 10h | 90% |
| 5 | $Na_2CO_3$ | DCM | 24h | n.r. |
| 6 | $Na_2CO_3$ | DMF | 24h | n.r. |
| 7 | $Na_2CO_3$ | $CH_3OH$ | 24h | n.r. |
| 8 | pyridine | HFIP | 24h | n.r. |
| 9 | DBU | HFIP | 24h | n.r. |
| 10 | TEA | HFIP | 24h | n.r. |
| 11 | $K_2CO_3$ | HFIP | 24h | 65% |
| 12 | NaOAc | HFIP | 24h | 70% |
| 13 | NaOH | HFIP | 24h | 56% |

[a] Reaction conditions: a mixture of **1a** (1.0 mmol), **2a** (1.1 mmol), and base (2 mmol) in solvent (2 mL) was stirred at room temperature for a certain period of time.

[b] Yield of isolated product.

**Table 1** Optimization of reaction conditions

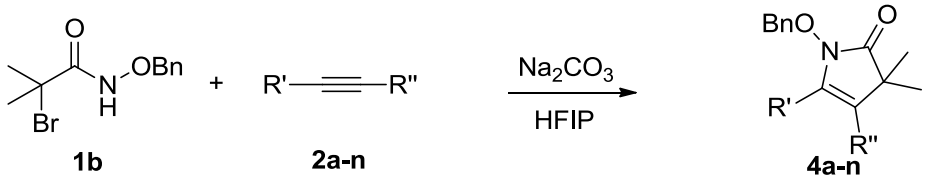
With the optimal conditions in hand, we next turned our attention to investigating the substrate scope and limitations of the [3+2] cycloaddition (Table 2-3). When α-haloamide **1a** was used to provide the aza-oxyallylic cation, different alkynes were tested under the optimal conditions. It was found that aryl alkynes provided the cycloaddition products in good to moderate yields (Table 2, 3a-3i). Electron withdrawing groups such as fluorine or chlorine and electron donating groups such as methoxyl, methyl, ethyl and *t*-butyl groups on the aromatic ring did not affect reaction yields. Electron donating heterocyclic aromatic rings, such as thiophene, also gave good yield (93%) of the product. However, pyridine and simple alkyl substituted alkynes did not provide any desired products (Table 2, 3l-3m). Also, when bulky internal alkynes were used in this reaction, no desired product formation was observed (Table 2, 3n).



| Entry | R' | R'' | Yield (%) |
|---|---|---|---|
| **3a** | Ph | H | 90 |
| **3b** | Ph | Me | 88 |
| **3c** | 4-Me-Ph | H | 85 |
| **3d** | 3-Me-Ph | H | 81 |
| **3e** | 4-Et-Ph | H | 83 |
| **3f** | 4-MeO-Ph | H | 89 |
| **3g** | 4-*t*Bu-Ph | H | 70 |
| **3h** | 4-F-Ph | H | 85 |
| **3i** | 2-Cl-Ph | H | 77 |
| **3j** | 2-Thiophenyl | H | 93 |
| **3k** | Cyclohex-1-enyl | H | 82 |
| **3l** | 2-Pyridinyl | H | 0 |
| **3m** | Et | H | 0 |
| **3n** | Ph | Ph | 0 |

**Table 2** Reactions of α-haloamide **1a** with alkynes

Not surprisingly, when α-haloamide **1b** was used to produce the aza-oxyallylic cation, the cycloaddition reaction also had a good substrate scope for different alkynes in good yields, except the **4d** and **4i**. We reasoned that the *ortho* (4i) and *meta* (4d) substitutes on the phenyl ring increased the steric hindrance which resulted in zero yield of the desired products.

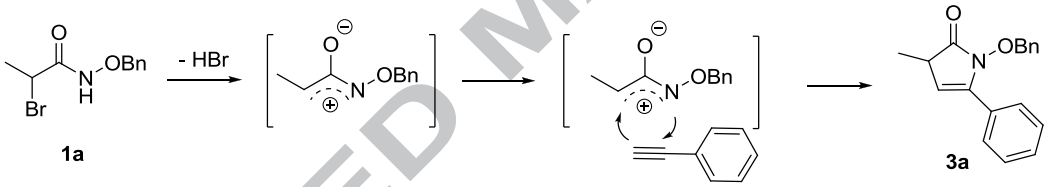



| Entry | R' | R'' | Yield (%) |
|---|---|---|---|
| **4a** | Ph | H | 82 |
| **4b** | Ph | Me | 76 |
| **4c** | 4-Me-Ph | H | 85 |
| **4d** | 3-Me-Ph | H | 0 |
| **4e** | 4-Et-Ph | H | 80 |
| **4f** | 4-MeO-Ph | H | 87 |

| | | | |
|---|---|---|---|
| **4g** | 4-*t*Bu-Ph | H | 67 |
| **4h** | 4-F-Ph | H | 85 |
| **4i** | 2-Cl-Ph | H | 0 |
| **4j** | 2-Thiophenyl | H | 89 |
| **4k** | Cyclohex-1-enyl | H | 84 |
| **4l** | 2-Pyridinyl | H | 0 |
| **4m** | Et | H | 0 |
| **4n** | Ph | Ph | 0 |

**Table 3** Reactions of α-haloamide **1b** with alkynes

The mechanism of this reaction is illustrated in scheme 2. First, α-haloamide is treated with HBr to generate aza-oxyallylic cation. The [3+2] cycloaddition of the resulting cation and dipolarophile alkyne produces product 3a. The excellent regiochemistry of this reaction can be explained by the steric effect of the unsymmetrical alkyne substrates and the substitutions on the aza-oxyallylic cation.




**Scheme 2** Proposed mechanism

**Conclusion**

In summary, a new synthetic method for functionalized 1,3-dihydro-2H-pyrrol-2-one was developed on the basis of a [3+2] cycloaddition reaction of aza-oxyallylic cations and alkynes. This reaction shows broad substrate scope and good functional group compatibility. Further studies on the synthesis of heterocycles using aza-oxyallylic cations are now in progress.[1]

**Acknowledgement**

The authors are grateful to the Education Department of Hubei province science and technology research project (Nos. Q20162803). This research was supported by the Doctoral Research Fund of Hubei University of Science and Technology (BK1434). The authors are also grateful to National Natural Science Foundation (21602053). This research was supported (in part)

by a grant from the Center for Research, College of Science and Health, William Paterson University of New Jersey.

**References**

[1] Barnes, K. L.; Koster, A. K.; Jeffrey, C. S. *Tetrahedron Lett*. **2014**, *55*, 4690.

[2] Kikugawa, Y.; Shimada, M.; Kato, M.; Sakamoto, T. *Chem. Pharm. Bull*. **1993**, *41*, 2192.

[3] Lengyel, I.; Sheehan, J. C. *Angew. Chem., Int. Ed.* **1968**, *7*, 25.

[4] (a) Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc*. **2011**, *133*, 7688. (b) Acharya, A.; Eickhoff, J. A.; Jeffrey, C. S. *Synthesis* **2013**, *45*, 1825

[5] (a) DiPoto, M. C.; Hughes, R. P.; Wu, J. *J. Am. Chem. Soc*. **2015**, *137*, 14861 (b) Ji, W. Z.; Yao, L. C.; Liao, X. B. *Org. Lett.* **2016**, *18*, 628.

[6] (a) Wu, Y. C.; Liu, L.; Wang, D.; Chen, Y. J. *J. Heterocycl. Chem.* **2006**, *43*, 949. (b) Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, *12*, 2843. (c) Nagarajan, A. S.; Reddy B. S. R. *Synthetic Commun.* **2013**, *43*, 1229.

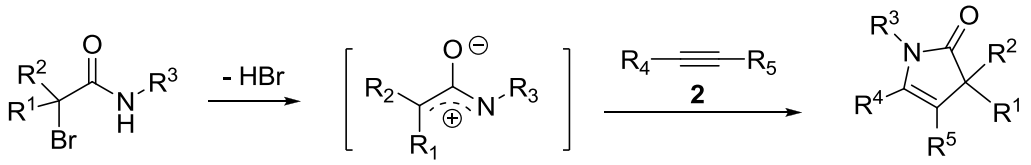
[7] (a) Alves, J. C. F. *J. Braz. Chem. Soc.* **2007**, *18*, 855. (b) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T.; *Tetrahedron: Asymmetry* **1998**, *9*, 1759.

[8] (a) Hussaini, S. R.; Moloney, M. G. *Org. Biomol. Chem.* **2006**, *4*, 2600. (b) Moloney, M. G.; Panchal, T.; Pike, R. *Org. Biomol.Chem.* **2006**, *4*, 3894. (b) Moloney, M. G. *Nat. Prod. Rep*. **2002**, *19*, 597. (c) Qiao, L.; Zhao, L. Y.; Rong, S. B.; Wu, X. W.; Wang, S.; Fujii, T.; Kazanietz, M. G.; Rauser, L.; Savage, J.; Roth, B. L.; Flippen-Anderson, J.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 955. (d) Wu, B.; Kuhen, K.; Nguyen, T. N.; Ellis, D.; Anaclerio, B.; He, X.; Yang, K.; Karanewsky, D.; Yin, H.; Wolff, K.; Bieza, K.; Caldwell, J.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3430. (e) Smith-III, A. B.; Charnley, A. K.; Harada, H.; Beiger, J. J.; Cantin, L. D.; Kenesky, C. S.; Hirschmann, R.; Munshi, S.; Olsen, D. B.; Stahlhut, M. W.; Schleif, W. A. ; Kuo, L. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 859.

[9] (a) Gurjar, M. K.; Joshi, R. A.; Chaudhuri, S. R.; Joshi, S. V.; Barde, A. R.; Gediya, L. K.; Ranade, P. V.; Kadam, S. M.; Naik, S. J. *Tetrahedron Lett.* **2003**, *44*, 4853. (b) Bishop, J. E.; Nagy, J. O.; O'Connell, J. F.; Rapoport, H. *J. Am. Chem. Soc.* **1991**, *113*, 8024. (c) Sabido, P. M. G.; Lightner, D. A. *Monatsh. Chem.* **2014**, *145*, 775. (d) Coffin, A. R.; Roussell, M. A.; Tserlin, E.; Pelkey, E. T. *J. Org. Chem.* **2006**, *71*, 6678. (e) Chavan, S. P.; Pathak, A. B.; Pawar, K. P. *Synthesis* **2015**, *47*, 955.

Highlights

- Efficient synthesis of functionalized 1,3-dihydro-2*H*-pyrrol-2-one
- [3+2] Cycloaddition reaction of aza-oxyallylic cations and alkynes
- Easy operation, ambient temperature, good yields
- Broad functional group tolerance




**1** **3**

$R_1$= $CH_3$, $R_2$= $CH_3$, H, $R_3$= OBn 78-92%

$R_4$= Ph, *p*-$CH_3$Ph, *p*-$CH_3$OPh, *p*-FPh, *m*-$CH_3$Ph, *o*-ClPh.... $R_5$= H, $CH_3$