Preliminary Communication

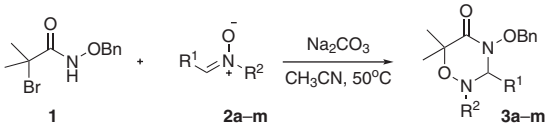
Rongxing Chen, Sen Zhao, Yueliuting Fu, Yiming Zhang, Haibing Guo, Gangqiang Wang*, Shaofa Sun* and Yalan Xing*

Highly efficient [3 + 3] cycloaddition reactions of *in situ* generated aza-oxyallyl cation with nitrones

https://doi.org/10.1515/hc-2018-0001
Received February 25, 2018; accepted February 27, 2018; previously published online March 30, 2018

Abstract: An efficient protocol was developed for the synthesis of 1,2,4-oxadiazinan-5-one derivatives via [3 + 3] cycloaddition of *in situ* generated aza-oxyallyl cations with nitrones. This method provides high yields of the heterocyclic products, excellent regioselectivity and broad substrate scope.

Keywords: aza-oxyallyl cations; cycloaddition; heterocycles; metal free; nitrones.



a: R^1 = Me; R^2 = Ph; 96%
b: R^1 = Me; R^2 = 2-Cl-C_6H_4; 80%
c: R^1 = Me; R^2 = 2-OMe-C_6H_4; 0%
d: R^1 = Me; R^2 = 3-Cl-C_6H_4; 89%
e: R^1 = Me; R^2 = 4-OMe-C_6H_4; 96%
f: R^1 = Me; R^2 = 4-NO_2-C_6H_4; 81%
g: R^1 = Me; R^2 = 2-naphthalenyl; 89%
h: R^1 = Me; R^2 = 3-styryl; 82%
i: R^1 = Me; R^2 = 2,4-diCl-C_6H_3; 85%
j: R^1 = Me; R^2 = thiophen-2-yl; 98%
k: R^1 = Me; R^2 = propyl; 77%
l: R^1 = Bn; R^2 = 4-Me-C_6H_4; 92%
m: R^1 = Bn; R^2 = thiophen-2-yl; 98%

Scheme 1

A number of medicinally important heterocycles have been prepared by [3 + 1], [3 + 2], [3 + 3], and [3 + 4] cycloadditions [1–12] of aza-oxyallylic cations with various synthons including alkynes, dienes and aldehydes. However, the [3 + 3] cycloadditions of aza-oxyallylic cations with nitrones have not received much attention until recently [6]. To the best of our knowledge, reference [6] is the only report of this type of synthesis of 1,2,4-oxadiazinan-5-ones. Nitrones are particularly useful for the construction of a variety of nitrogen- and oxygen-containing five and six-membered heterocycles [13–19].

As part of our effort to develop efficient synthetic methodologies for the synthesis of heterocyclic molecules [19, 20], we wish to report the synthesis of 1,2,4-oxadiazinan-5-ones via [3 + 3] cycloaddition of *in situ* generated an aza-oxyallyl cation with nitrones. The aza-oxyallyl cation is easily generated from *N*-(benzyloxy)-2-bromo-2-methylpropanamide (**1** in Scheme 1). Compared to Wang's report [6], our method utilizes simple and readily available inorganic base Na_2CO_3 instead of 4-dimethylaminopyridine (DMAP) used in Wang's reaction. Acetonitrile was employed as a solvent in our method in contrast to the more expensive hexafluoro-2-propanol used in Wang's reaction.

The reaction of **1** and nitrone **2a** was investigated as a model [3 + 3] cycloaddition (Scheme 1). The desired 1,2,4-oxadiazinan-5-one 3**a** was obtained in a 98% yield using Na_2CO_3 as the base and acetonitrile as the solvent at 50°C. The use of other bases including K_2CO_3, NaOAc, NaOH, pyridine, DBU and TEA resulted in a greatly diminished yield of **3a**. Also, only a trace amount of the product was isolated for the reaction conducted in MeOH, CF_3CH_2OH, DMF, THF or DCM. It is worth mentioning that the use of Wang's solvent gave only a moderate yield of **3a** of 65%. Under the optimized conditions, the use of other substrates **2b** and **2d–m** gave good to excellent yields of products **3** ranging from 77% to 98%. The only exception was a failed synthesis of **3c** which, apparently, is due to the steric hindrance in the starting nitrone **2c**.

Experimental

^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were taken in $CDCl_3$ at 400 MHz and 100 MHz, respectively. Mass spectra were obtained using the electrospray ionization (ESI) mode. Nitrones **2a–m** were prepared as previously reported [6]. All products **3a–m** are colorless oils.

***Corresponding authors: Gangqiang Wang and Shaofa Sun,** Non-Power Nuclear Technology Collaborative Innovation Center, School of Nuclear Technology, Chemistry and Biology, Hubei University of Science and Technology, Xianning 437100, China, e-mail: wgq2008@163.com (G. Wang); sunshaofa@mail.hbust.com.cn (S. Sun); and **Yalan Xing,** Department of Chemistry, William Paterson University of New Jersey, 300 Pompton Road, Wayne, NJ 07470, USA, e-mail: xingy@wpunj.edu
Rongxing Chen, Sen Zhao, Yueliuting Fu, Yiming Zhang and Haibing Guo: Non-Power Nuclear Technology Collaborative Innovation Center, School of Nuclear Technology, Chemistry and Biology, Hubei University of Science and Technology, Xianning 437100, China

General procedure for synthesis of substrate 1

The following modification of the previously reported procedure was used [6]. A mixture of *O*-benzylhydroxylamine hydrochloride (1 g, 6.3 mmol) and triethylamine (0.88 mL, 6.3 mmol) in dichloromethane (30 mL) was cooled to 0°C and treated dropwise with 2-bromo-2-methylpropanoyl bromide (0.75 mL, 6.3 mmol). The mixture was stirred for 4 h at 0°C, then quenched with water and washed with brine (×3). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with ethyl acetate/hexanes to give haloamide **1** as a white solid; yield 1.3 g (80%).

Synthesis of 3a,b and 3d–m

A mixture of nitrone **2** (1.1 mmol), haloamide **1** (1.0 mmol) and sodium carbonate (2 mmol) in acetonitrile (20 mL) was stirred at 50°C, and the reaction progress was monitored by silica gel TLC eluting with hexanes/ethyl acetate, 5:1. The mixture was filtered through the short pad of celite, and the filtrate was concentrated under reduced pressure. The residue of **3** was purified by silica gel chromatography eluting with hexanes/ethyl acetate, 10:1.

4-(Benzyloxy)-3,6,6-trimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3a) Yield 96%; ^{1}H NMR: δ 7.47–7.38 (m, 5H), 7.32–7.28 (m, 3H), 7.13–7.11 (m, 2H), 5.00 (d, 1H, *J* = 10 Hz), 4.89 (s, 1H), 4.40 (d, 1H, *J* = 10 Hz), 2.35 (s, 3H), 1.71 (s, 3H), 1.51 (s, 3H); ^{13}C NMR: δ 170.6, 134.7, 133.9, 129.9, 129.8, 129.1, 128.8, 128.6, 128.4, 81.8, 77.1, 41.3, 24.1, 23.9. HR-MS. Calcd for $C_{19}H_{22}N_2O_3Na$, $[M+Na]^+$: *m*/*z* 349.1528. Found: *m*/*z* 349.1525.

4-(Benzyloxy)-2-(2-chlorophenyl)-3,6,6-trimethyl-1,2,4-oxadiazinan-5-one (3b) Yield 80%; ^{1}H NMR: δ 7.45 (s, 1H), 7.44–7.42 (m, 1H), 7.35–7.30 (m, 6H), 7.28–7.23 (s, 2H), 5.02 (d, 1H, J = 10 Hz), 4.89 (s, 1H), 4.65 (d, 1H, J = 10 Hz), 2.42 (s, 3H), 1.62 (s, 3H), 1.53 (s, 3H); ^{13}C NMR: δ 170.4, 134.9, 134.5, 130.6, 130.5, 129.7, 128.8, 128.4, 127.2, 82.0, 70.0, 40.7, 24.0. HR-MS. Calcd for $C_{19}H_{21}ClN_2O_3Na$, $[M+Na]^+$: *m*/*z* 383.1138). Found: *m*/*z* 383.1136.

4-(Benzyloxy)-2-(3-chlorophenyl)-3,6,6-trimethyl-1,2,4-oxadiazinan-5-one (3d) Yield 89%; ^{1}H NMR: δ 7.43–7.15 (m, 9H), 4.99 (d, 1H, J = 10 Hz), 4.80 (s, 1H), 4.48 (d, 1H, J = 10 Hz), 2.33 (s, 3H), 1.68 (s, 3H), 1.51 (s, 3H); ^{13}C NMR: δ 170.4, 136.0, 134.7, 134.5, 130.0, 129.9, 129.0, 128.5, 127.3, 82.0, 77.2, 41.4, 24.0, 23.9. HR-MS. Calcd for $C_{19}H_{21}ClN_2O_3Na$, $[M+Na]^+$: *m*/*z* 383.1138. Found: *m*/*z* 383.1136.

4-(Benzyloxy)-2-(4-methoxyphenyl)-3,6,6-trimethyl-1,2,4-oxadiazinan-5-one (3e) Yield 96%; ^{1}H NMR: δ 7.32-7.28 (m, 5H), 7.16–7.14 (m, 2H), 6.94 (d, 2H, J = 9 Hz), 4.98 (d, 1H, J = 10 Hz), 4.83 (s, 1H), 4.42 (d, 1H, J = 10 Hz), 3.86 (s, 3H), 2.33 (s, 3H), 1.69 (s, 3H), 1.50 (s, 3H); ^{13}C NMR: δ 170.4, 160.7, 134.9, 130.3, 129.8, 128.8, 128.4, 126.0, 113.9, 81.8, 77.1, 55.4, 41.3, 24.1, 24.0. HR-MS. Calcd for $C_{20}H_{24}N_2O_4Na$, $[M+Na]^+$: *m*/*z* 379.1634. Found: *m*/*z* 379.1635.

4-(Benzyloxy)-3,6,6-trimethyl-2-(4-nitrophenyl)-1,2,4-oxadiazinan-5-one (3f) Yield 81%; ^{1}H NMR: δ 8.23 (d, 2H, J = 9 Hz), 7.45 (d, 2H, J = 9 Hz), 7.36–7.28 (m, 3H), 7.17–7.14 (m, 2H), 4.97 (d, 1H, J = 10 Hz), 4.89 (s, 1H), 4.57 (d, 1H, J = 10 Hz), 2.29 (s, 3H), 1.66 (s, 3H), 1.52 (s, 3H); ^{13}C NMR: δ 170.4, 148.7, 140.8, 134.7, 130.0, 129.8, 129.1, 128.5, 123.7, 82.3, 77.1, 41.2, 23.9. HR-MS. Calcd for $C_{19}H_{21}N_3O_5Na$, $[M+Na]+$: *m*/*z* 394.1379. Found: *m*/*z* 394.1378.

4-(Benzyloxy)-3,6,6-trimethyl-2-(naphthalen-2-yl)-1,2,4-oxadiazinan-5-one (3g) Yield 89%; ^{1}H NMR: δ 7.93–7.88 (m, 3H), 7.75–7.56 (m, 4H), 7.31–7.24 (m, 3H), 7.07 (d, 2H, J = 7 Hz), 5.04 (d, 1H, J = 10 Hz), 5.01 (s, 1H), 4.44 (d, 1H, J = 10 Hz), 2.38 (s, 3H), 1.78 (s, 3H), 1.57 (s, 3H); ^{13}C NMR: δ 170.5, 134.8, 134.1, 132.9, 131.4, 129.9, 128.9, 128.6, 128.4, 128.2, 127.9, 126.0, 125.6, 82.0, 77.2, 41.5, 24.1, 24.0. HR-MS. Calcd for $C_{23}H_{24}N_2O_3Na$, $[M+Na]^+$: *m*/*z* 399.1690. Found: *m*/*z* 399.1685.

(*E*)-4-(Benzyloxy)-3,6,6-trimethyl-2-styryl-1,2,4-oxadiazinan-5-one (3h) Yield 82%; ^{1}H NMR: δ 7.43–7.28 (m, 10H), 6.58 (d, 1H, J = 15 Hz), 5.04 (d, 1H, J = 10 Hz), 4.86 (d, 1H, J = 10 Hz), 4.53 (d, 1H, J = 10 Hz), 2.53 (s, 3H), 1.52 (s, 3H), 1.50 (s, 3H); ^{13}C NMR: δ 170.1, 138.0, 135.4, 134.9, 130.0, 128.8, 128.4, 127.0, 122.0, 82.0, 77.4, 41.3, 24.0, 23.8. HR-MS. Calcd for $C_{21}H_{24}N_2O_3Na$, $[M+Na]^+$: *m*/*z* 375.1685. Found: *m*/*z* 375.1683.

4-(Benzyloxy)-2-(2,4-dichlorophenyl)-3,6,6-trimethyl-1,2,4-oxadiazinan-5-one (3i) Yield 85%; ^{1}H NMR: δ 7.36–7.28 (m, 5H), 7.44–7.43 (m, 2H), 7.34–7.24 (m, 6H), 5.73 (s, 1H), 5.00 (d, 1H, J = 10 Hz), 4.70 (d, 1H, J = 10 Hz), 2.40 (s, 3H), 1.63 (s, 3H), 1.52 (s, 3H); ^{13}C NMR: δ 170.7, 135.9, 135.5, 134.4, 131.3, 129.7, 129.4, 129.0, 128.5, 127.7, 82.2, 77.0, 40.6, 23.9, 23.8. HR-MS. Calcd for $C_{19}H_{20}Cl_2N_2O_3Na$, $[M+Na]^+$: *m*/*z* 417.0749. Found: *m*/*z* 417.0750.

4-(Benzyloxy)-3,6,6-trimethyl-2-(thiophen-2-yl)-1,2,4-oxadiazinan-5-one (3j) Yield 98%; ^{1}H NMR: δ 7.46–7.06 (m, 8H), 5.31 (s, 1H), 5.04 (d, 1H, J = 10.1Hz), 4.45 (d, 1H, J = 10Hz), 2.43 (s, 3H), 1.61 (s, 3H), 1.58 (s, 3H); ^{13}C NMR: δ 169.8, 134.8, 129.7, 128.8, 128.5, 128.4, 128.2, 126.2, 82.3, 77.6, 41.0, 24.0, 23.5. HR-MS. Calcd for $C_{17}H_{20}N_2O_3SNa$, $[M+Na]^+$: *m*/*z* 355.1092. Found: *m*/*z* 355.1090.

4-(Benzyloxy)-3,6,6-trimethyl-2-propyl-1,2,4-oxadiazinan-5-one (3k) Yield 77%; ^{1}H NMR: δ 7.47–7.39 (m, 5H), 4.97 (s, 2H), 4.00 (t, 1H, J = 3.7 Hz), 2.57 (s, 3H), 1.93–1.75 (m, 2H), 1.56–1.40 (m, 8H), 0.90 (t, 3H, J = 7 Hz); ^{13}C NMR: δ 170.3, 135.0, 129.9, 129.0, 128.6, 83.2, 81.5, 76.5, 41,3, 30.6, 24.1, 23.5, 14.2. HR-MS. Calcd for $C_{16}H_{24}N_2O_3Na$, $[M+Na]^+$: *m*/*z* 315.1685. Found: *m*/*z* 315.1681.

2-Benzyl-4-(benzyloxy)-6,6-dimethyl-3-(*p*-tolyl)-1,2,4-oxadiazinan-5-one (3l) Yield 92%; ^{1}H NMR: δ 7.40–7.17 (m, 14H), 5.09 (s, 1H), 5.03 (d, 1H, J = 10Hz), 4.45 (d, 1H, J = 10 Hz), 3.63 (d, 1H, J = 10 Hz), 3.45 (d, 1H, J = 10 Hz), 2.44 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H); ^{13}C NMR: δ 170.5, 139.8, 136.4, 134.9, 131.1, 130.3, 129.8, 129.4, 129.3, 129.1, 128.8, 128.6, 128.4, 128.0, 127.4, 81.8, 77.1, 57.2, 24.0, 23.8, 21.4. HR-MS. Calcd for $C_{26}H_{28}N_2O_3Na$, $[M+Na]+$: *m*/*z* 439.1998. Found: *m*/*z* 439.1995.

2-Benzyl-4-(benzyloxy)-6,6-dimethyl-3-(thiophen-2-yl)-1,2,4-oxadiazinan-5-one (3m) Yield 98%; ^{1}H NMR: δ 7.51–7.09 (m, 13H), 5.41 (s, 1H), 5.03 (d, 1H, J = 10 Hz), 4.44 (d, 1H, J = 10 Hz), 3.80 (d, 1H, J = 10 Hz), 3.52 (d, 1H, J = 10 Hz), 1.50 (s, 3H), 1.48 (s, 3H); ^{13}C NMR: δ 170.0, 134.6, 130.0, 129.7, 129.4, 128.9, 128.5, 128.4, 128.3, 127.8, 126.2, 82.5, 77.7, 57.3, 23.9, 23.3. HR-MS. Calcd for $C_{23}H_{24}N_2O_4SNa$, $[M+Na]^+$: *m*/*z* 431.1405. Found: *m*/*z* 431.1400.

Acknowledgment: This work was supported by grants of the Hubei Provincial Department of Education (T201419), National Natural Science Foundation (21602053) and Center for Research, College of Science and Health, William Paterson University of New Jersey.

References

[1] Li, C.; Jiang, K.; Ouyang, Q.; Liu, T.-Y.; Chen, Y.-C. [3 + 1]- and [3 + 2]-cycloadditions of azaoxyallyl cations and sulfur ylides. *Org. Lett.* **2016**, *18*, 2738–2741.

[2] Acharya, A.; Anumandla, D.; Jeffrey, C. S. Dearomative indole cycloaddition reactions of aza-oxyallyl cationic intermediates: modular access to pyrroloindolines. *J. Am. Chem. Soc.* **2015**, *137*, 14858–14860.

[3] Acharya, A.; Montes, K.; Jeffrey, C. S. Access to 4-oxazolidinones: A (3 + 2) cycloaddition approach. *Org. Lett.* **2016**, *18*, 6082–6085.

[4] Ji, W.; Yao, L.; Liao, X. Access to the pyrroloindoline core via [3 + 2] annulation as well as the application in the synthetic approach to (±)-minfiensine. *Org. Lett.* **2016**, *18*, 628–630.

[5] Jia, Q.; Du, Z.; Zhang, K.; Wang, J. [3 + 2] Cycloaddition of aza-oxyallyl cations with aldehydes. *Org. Chem. Front.* **2017**, *4*, 91–94.

[6] Jia, Q.; Li, D.; Lang, M.; Zhang, K.; Wang, J. 4-Dimethylaminopyridine-mediated [3 + 3] cycloaddition of aza-oxyallyl cations and nitrones. *Adv. Synth. Catal.* **2017**, *359*, 3837–3842.

[7] Barnes, K. L.; Koster, A. K.; Jeffrey, C. S. Trapping the elusive aza-oxyallylic cation: new opportunities in heterocycloaddition chemistry. *Tetrahedron Lett.* **2014**, *55*, 4690–4696.

[8] Acharya, A.; Eickhoff, J. A.; Chen, K.; Catalano, V. J.; Jeffrey, C. S. Access to bicyclic hydroxamate macrocycles via intramolecular aza-(4 + 3) cyloaddition reactions of aza-oxyallylic cation intermediates. *Org. Chem. Front.* **2016**, *3*, 330–334.

[9] Acharya, A.; Eickhoff, J. A.; Jeffrey, C. S. Intramolecular aza-[4 + 3] cycloaddition reactions of α-halohydroxamates. *Synthesis* **2013**, *45*, 1825–1836.

[10] Anumandla, D.; Jeffrey, C. S. Oxidative 1,4-diamination of dienes using simple urea derivatives. *Org. Lett.* **2014**, *16*, 5112–5115.

[11] Barnes, K. L.; Chen, K.; Catalano, V. J.; Jeffrey, C. S. New building blocks for iminosugars: a concise synthesis of polyhydroxylated N-alkoxypiperidines through an intramolecular azepine ring contraction. *Org. Chem. Front.* **2015**, *2*, 497–501.

[12] Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. Generation and reactivity of aza-oxyallyl cationic intermediates: aza-[4 + 3] cycloaddition reactions for heterocycle synthesis. *J. Am. Chem. Soc.* **2011**, *133*, 7688–7691.

[13] Ferrier, R. J. Miscellaneous nitrogen-containing derivatives. *Carbohydr. Chem.* **2003**, *34*, 136–156.

[14] Huple, D. B.; Ghorpade, S.; Liu, R.-S. Recent advances in gold-catalyzed N- and O-functionalizations of alkynes with nitrones, nitroso, nitro and nitroxy species. *Adv. Synth. Catal.* **2016**, *358*, 1348–1367.

[15] Seebach, D.; Sting, A. R.; Hoffmann, M. Catalytic asymmetric alkylation of nucleophiles: asymmetric synthesis of α-alkylated amino acids. *Angew. Chem., Int. Ed. Engl.* **1997**, *35*, 2708–2748.

[16] Ulgen, M.; Sevinc, N. Studies on the metabolism of nitrogen compounds by Prof J. W. Gorrod. *Curr. Drug Metab.* **2017**, *18*, 291–305.

[17] 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 Lett.* **2017**, *58*, 847–850.

[18] Wang, G.; Zhao, S.; Chen, R.; Yang, L.; Wang, J.; Guo, H.; Wu, M.; Domena, J.; Xing, Y.; Sun, S. Synthesis of thiazolidin-4-ones via [3 + 2] cycloaddition of in situ generated aza-oxyallylic cations with isothiocyanates. *Tetrahedron Lett.* **2017**, *58*, 4308–4311.

[19] Jiang, L.; Tao, G.; Li, Z.; Sun, S.; Kim, C.; Huang, C.; Guo, H.; Jian, W.; Xing, Y. Highly regioselective dipolar cycloadditions of nitrile oxides with α,β-acetylenic aldehydes. *Tetradedron Lett.* **2016**, *57*, 712–714.

[20] Yang, X.; Wu, M.; Sun, S.; Huang, C.; Guo, H.; Jian, W.; Lee. J.; Xing, Y. Synthesis of tricyclic quinazolinones via intramolecular cyclization of 3-(2-aminoalkyl)-2-(phenylamino)quinazolin-4(3*H*)-ones. *Mol. Diversity*. **2016**, *20*, 551–556.