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Addition of Cyclic Ureas and 1-Methyl-2-oxazolidone to Pyridynes: A New Approach to Pyridodiazepines, Pyridodiazocines, and Pyridooxazepines

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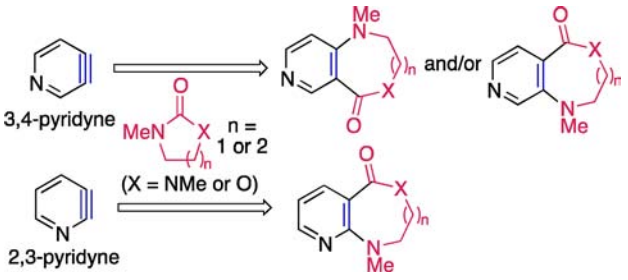
ABSTRACT



Reactions of pyridynes with cyclic urea and 1-methyl-2-oxazolidone were demonstrated. 3,4-Pyridyne and 2,3-pyridyne were reacted with *N*,*N*-dimethylimidazolidone, *N*,*N*-dimethylpropylene urea, and 1-methyl-2-oxazolidone to give the corresponding pyridodiazepines, pyridodiazocines, and pyridooxazepines, respectively.

Benzyne (Figure 1, **1**) has been recognized as a useful synthon in organic chemistry, and a number of synthetic utilizations of benzynes including natural product synthesis have been demonstrated to date.[1] Pyridynes, nitrogen-containing analogs of benzyne, are classified as 3,4-pyridynes (**2**) and 2,3-pyridynes (**3**) according to the position of the triple bond in the pyridine ring, and pyridynes are also expected to be useful synthetic units, especially for the preparation of polysubstituted pyridine derivatives. However, in contrast to extensive studies on benzyne chemistry in organic synthesis, synthetic utilization of pyridynes has been limited. Therefore, the development of a new method for the transformation of pyridyne remains a frontier in modern organic chemistry.[2] In this context, we have recently developed a new synthetic methodology for polysubstituted isoquinolines via a nickel-catalyzed [2 + 2 + 2] cycloaddition of 3,4-pyridynes and diynes, in which the triple bond in 3,4-pyridyne was utilized as a reactive alkyne.[3]

In 2002, Hiyama reported that the reaction of benzyne (**1**) and *N*,*N*-dimethylimidazolidone (DMI, **5**) afforded

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(1) (a) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (c) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (d) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199. (e) Bhunia, A.; Yetra, R. S.; Biju, T. A. *Chem. Soc. Rev.* **2012**, *41*, 3140. (f) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (g) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (h) Yoshida, H.; Takaki, K. *Synlett* **2012**, *23*, 1725.

(2) For recent reports on the use of pyridyne in the organic synthesis, see: (a) Jiang, L.; Yu, X.; Fang, B.; Wu, J. *Org. Biomol. Chem.* **2012**, *10*, 8102. (b) Fang, Y.; Larock, R. C. *Tetrahedron* **2012**, *68*, 2819. (c) Enamorado, M. F.; Ondachi, P. W.; Comins, D. L. *Org. Lett.* **2010**, *12*, 4513. (d) Lin, W.; Chen, L.; Knochel, P. *Tetrahedron* **2007**, *63*, 2787. (e) Connon, S. J.; Hegarty, A. F. *Eur. J. Org. Chem.* **2004**, 3477. (f) Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 5789. (g) Connon, S. J.; Hegarty, A. F. *Tetrahedron Lett.* **2001**, *42*, 735. (h) Connon, S. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245.

(3) (a) Iwayama, T.; Sato, Y. *Chem. Commun.* **2009**, 5245. (b) Iwayama, T.; Sato, Y. *Heterocycles* **2010**, *80*, 917.

10.1021/ol303352q

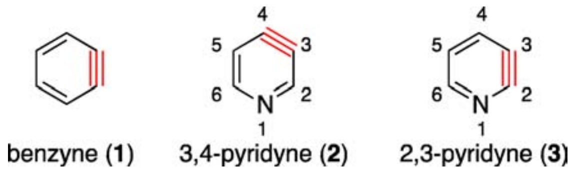
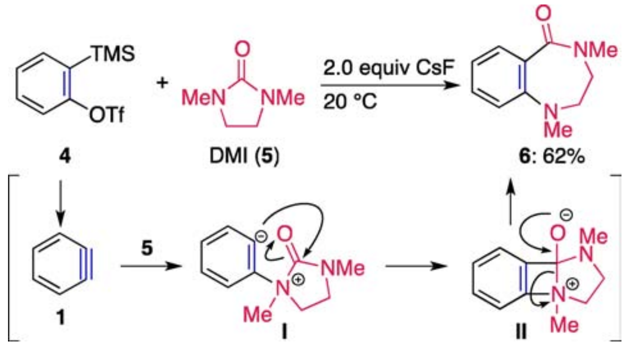


Figure 1. Benzyne (**1**) and pyridynes (**2** and **3**).

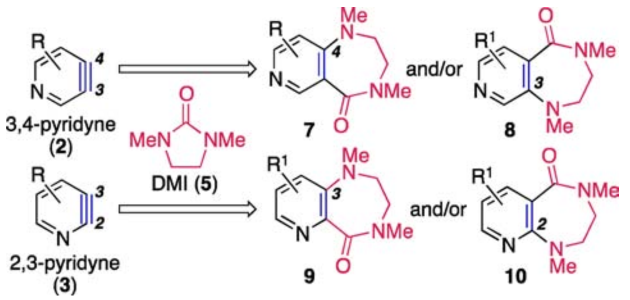
benzodiazepine derivative **6** in good yield (Scheme 1).[4] Generally, benzynes have a lower LUMO level and higher HOMO level than those of normal alkynes, and the triple bond in benzynes was utilized as both an electrophile and a nucleophile in this reaction.[5] Nucleophilic addition of a nitrogen atom of DMI (**5**) to the triple bond of benzyne (**1**) generated from the precursor **4** and CsF[6] initially occurred to give the intermediate **I**. Then intramolecular nucleophilic attack of the carbanion of **I** to the amide carbonyl group gave **II**, from which ring expansion proceeded to give the product **6**.

Scheme 1. Synthesis of Benzodiazepine via Coupling of Benzyne and DMI



With this as a background, we envisaged that if the reaction of 3,4-pyridyne (**2**) and 2,3-pyridyne (**3**) with DMI (**5**) also proceeds in a manner similar to that of the above benzyne case, pyridodiazepine derivatives **7**−**10** would be obtained (Scheme 2).[7] Some compounds including a pyridodiazepine structure exert important biological activity,[8] and the development of a new method for preparation of pyridodiazepines is therefore of interest to the medicinal chemistry field.[9]

Scheme 2. Planned Synthesis of Pyridodiazepine Derivatives via Coupling of Pyridynes and DMI



To examine the feasibility of this plan, a 3,4-pyridyne precursor, 4-triethylsilyl-3-trifluoromethanesulfonyloxypyridine (**11a**), was reacted with DMI in the presence of CsF.[10] As a result, the expected pyridodiazepine derivatives **7a** and **8a** were obtained in a total yield of 86% in a ratio of 65% to 35% (Scheme 3).[11,12] The coupling product

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(4) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247.

(5) For most recent examples of the reaction of benzyne with a nucleophile and an electrophile, see: (a) Okuma, K.; Itoyama, R.; Sou, A.; Nagahora, N.; Shioji, K. *Chem. Commun.* **2012**, *48*, 11145. (b) Ma, X.; Chen, Y.; Zhang, Y.; Xu, D.; Cao, W.; Chen, J. *Eur. J. Org. Chem.* **2012**, 1388. (c) Fang, Y.; Rogness, D. C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 6262. (d) Ren, H.; Wu, C.; Ding, X.; Chen, X.; Shi, F. *Org. Biomol. Chem.* **2012**, *10*, 8975. (e) Kovács, S.; Csincsi, A. I.; Zs. Nagy, T.; Boros, S.; Timári, G.; Novák, Z. *Org. Lett.* **2012**, *14*, 2022. (f) Stokes, S.; Bekkam, M.; Rupp, M.; Mead, K. T. *Synlett* **2012**, *23*, 389. (g) Kim, J.; Stoltz, B. M. *Tetrahedron Lett.* **2012**, *53*, 4994. (h) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji., K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822. (i) Diemer, V.; Begaud, M.; Leroux, F. R.; Colobert, F. *Eur. J. Org. Chem.* **2011**, 341. (j) Łączkowski, K. Z.; García, D.; Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Org. Lett.* **2011**, *13*, 960. (k) Ikawa, T.; Nishiyama, T.; Nosaki, T.; Takagi, A.; Akai, S. *Org. Lett.* **2011**, *13*, 1730. (l) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946. (m) Chai, G.; Qiu, Y.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 5196. (n) Alajarin, M.; Lopez-Leonardo, C.; Raja, R.; Orene, R.-A. *Org. Lett.* **2011**, *13*, 5668.

(6) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(7) For recent reports on the synthesis of pyridodiazepine, see: (a) Bouakher, A. E.; Laborie, H.; Aadil, M.; Hakmaoui, A. E.; Lazar, S.; Akssira, M.; Viaud-Massuard, M.-C. *Tetrahedron Lett.* **2011**, *52*, 5077. (b) Van den Bogaert, A. M.; Nelissen, J.; Ovaere, M.; Van Meervelt, L.; Compernolle, F.; De Borggraeve, W. M. *Eur. J. Org. Chem.* **2010**, 5397. (c) Bonacorso, H. G.; Lourega, R. V.; Porte, L. M. F.; Deon, E. D.; Zanatta, N.; Flores, A. F. C.; Martins, M. A. P. *J. Heterocycl. Chem.* **2009**, *46*, 603. (d) Goswami, S.; Hazra, A.; Jana, S. *J. Heterocycl. Chem.* **2009**, *46*, 861. (e) Ramnauth, J.; Surman, M. D.; Sampson, P. B.; Forrest, B.; Wilson, J.; Freeman, E.; Manning, D. D.; Martin, F.; Toro, A.; Domagala, M.; Awrey, D. E.; Bardouniotis, E.; Kaplan, N.; Berman, J.; Pauls, H. W. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5359. (f) Geng, B.; Basarab, G.; Comita-Prevoir, J.; Gowravaram, M.; Hill, P.; Kiely, A.; Loch, J.; MacPherson, L.; Morningstar, M.; Mullen, G.; Osimboni, E.; Satz, A.; Eyermann, C.; Lundqvist, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 930. (g) Magano, J.; Acciacca, A.; Akin, A.; Collman, B. M.; Conway, B.; Waldo, M.; Chen, M. H.; Mennen, K. E. *Org. Process Res. Dev.* **2009**, *13*, 555. (h) Bonacorso, H. G.; Lourega, R. V.; Righi, F. J.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **2008**, *45*, 1679. (i) Bonacorso, H. G.; Lourega, R. V.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2007**, *48*, 4835. (j) Donati, D.; Ferrini, S.; Fusi, S.; Ponticelli, F. *Synthesis* **2003**, 2518.

(8) For example, pirenzepine (Gastrozepin, CAS Registry No. 28797-61-7), a representative M_1 antagonist, includes a pyrido[2,3-*b*][1,4]-diazepine structure. Furthermore, nevirapine, one of the most common HIV medicines (Viramune, CAS Registry No. 129618-40-2) has a dipyridodiazepine skeleton. For recent examples of synthesis and biological evaluation of pyridodiazepine derivatives, see: References 7e−7g.

(9) During the preparation of this manuscript, the same approach to pyridodiazepines from 3,4-pyridyne and *N*,*N*,-dimethylimidazolidone was demonstrated by Garg's group. See: Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5*, 54.

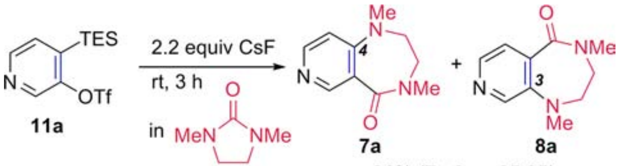
(10) For the synthesis of 4-trialkylsilyl-3-trifluoromethanesulfonyloxypyridine (3,4-pyridyne precursor) and generation of 3,4-pyridyne from the precursor and fluoride ion, see: Tsukazaki, M.; Snieckus, V. *Heterocycles* **1992**, *33*, 533.

(11) The structures of the products were determined by NOE experimens. See Supporting Information.

(12) Similar selectivity was observed in the reaction of 3-trifluoromethanesulfonyl-4-trimethylsilylpyridine and DMI reported by Garg. See ref 9.

7a should be produced via nucleophilic addition of DMI to the 4-position of pyridyne, while the regioisomer **8a** should be obtained via addition of DMI to the 3-position of 3,4-pyridynes.

Scheme 3. Reaction of 3,4-Pyridyne and DMI

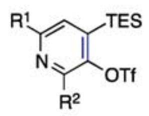
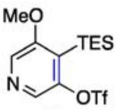
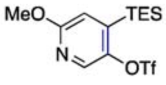


11a **7a** **8a**

86% (**7a**:**8a** = 65:35)

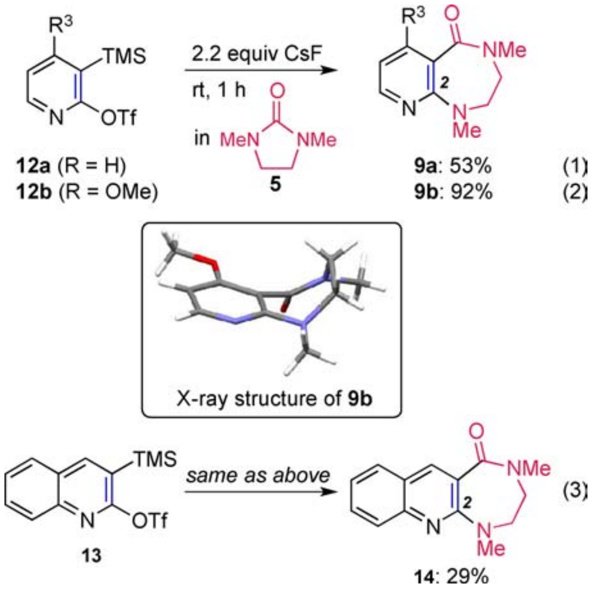
In order to improve the regioselectivity, introduction of a substituent into an appropriate position of the pyridine ring was investigated.[13] Thus, the 3,4-pyridyne precursor **11b**, having a methoxy group at the 2-position of the pyridine ring, was treated with CsF in DMI (Table 1, run 1). As expected, pyridodiazepine **7b** was produced as a single isomer in high yield in a regioselective manner. 2,6-Dimethoxy-3,4-pyridyne **11c** also reacted with DMI in a highly regioselective manner, giving **7c** in 90% yield (run 2). The amide group at the 2-position (**11d**) also affected the regioselectivity, the coupling product **7d** being obtained in 82% yield (run 3). When the precursor **11e** was used, the reaction proceeded to give the corresponding pyridodiazepine **8e** in high yield through nucleophilic addition of DMI to the 3-position (run 4). On the other hand, the regioselectivity was lost when the precursor **11f** having a methoxy group at the 6-position was used (run 5). These results indicated that the introduction of substituents to an appropriate position on the pyridine ring is requisite for the achievement of high regioselectivity.

Table 1. Reaction of Substituted-3,4-Pyridynes and DMI[a]

run	pyridyne precursors	product
		
1	**11b** (R^1 = H, R^2 = OMe)	**7b**: 91%
2	**11c** (R^1 = R^2 = OMe)	**7c**: 90%
3	**11d** (R^1 = H, R^2 = CONEt$_2$)	**7d**: 82%
4	 **11e**	 **8e**: 94%
5	 **11f**	 **7f** **8f** 96% (**7f**:**8f** = 60:40)

[a] Conditions: CsF (2.2 equiv), [**11**] = 0.5 M in DMI, rt, reaction time: 3 h (runs 1−3 and 5), 6 h (run 4).

Scheme 4. Reaction of 2,3-Pyridynes with DMI



12a (R = H)
12b (R = OMe)
5
9a: 53% (1)
9b: 92% (2)
13
14: 29% (3)

We also investigated the coupling reaction of 2,3-pyridyne and DMI (Scheme 4). The 2,3-pyridyne precursor **12a** was treated with CsF[14] in DMI at room temperature, giving pyridodiazepine **9a** in 53% yield as a single regioisomer (eq 1). The reaction of **12b** having a methoxy group at the 4-position with DMI gave the corresponding diazepine derivative **9b** in high yield (eq 2). The structure of the new pyridodiazepine was unambiguously determined by X-ray crystallographic analysis of **9b**.[15] Furthermore, 2,3-quinolyne precursor **13** also reacted with DMI in the presence of CsF in a regioselective manner to give the tricyclic product **14**, although the yield was lower compared to the reaction of 2,3-pyridyne (eq 3).

Next, we turned our attention to the use of *N*,*N*-dimethylpropylene urea (DMPU, **15**) instead of DMI for the reaction with pyridynes (Scheme 5). Thus, 3,4-pyridyne precursors **11a**, **11b**, and **11e** were treated with CsF in DMPU, giving the corresponding pyridodiazocine derivatives in moderate yields.[16] In this case, the existence of a methoxy group again affected the regioselectivity of the

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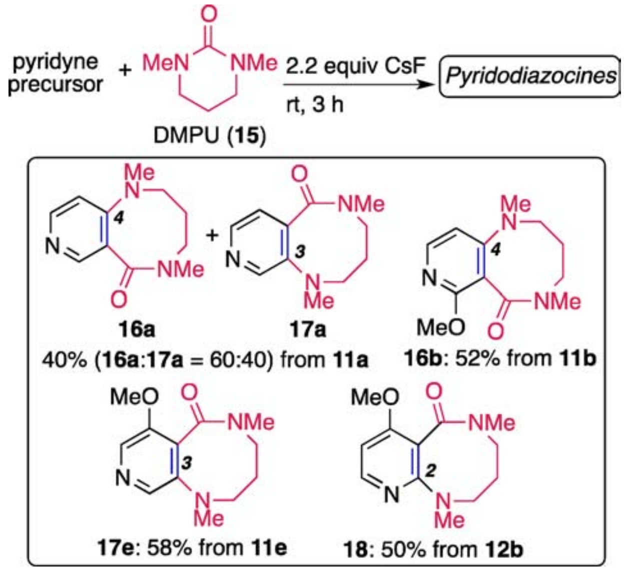
[13] It is known that introduction of substituents into the 2- or 5-position of the pyridine ring improves the regioselectivity of the first nucleophilic addition step to 3,4-pyridyne. See: (a) den Hertog, H. J.; Pieterse, M. J.; Buurman, D. J. *Recl. Trav. Chim. Pays−Bas* **1963**, *82*, 1173. (b) Martens, R. J.; den Hertog, H. J. *Recl. Trav. Chim. Pays−Bas* **1964**, *83*, 621. (c) Pieterse, M. J.; den Hertog, H. J. *J. South African Chem. Inst.* **1964**, *17*, 41. See also ref 9.

[14] For the synthesis of 3-trialkylsilyl-2-trifluoromethanesulfonyloxypyridine (2,3-pyridyne precursor) and generation of 2,3-pyridyne from the precursor and a fluoride source, see: (a) Walters, M. A.; Shay, J. J. *Synth. Commun.* **1997**, *27*, 3573. (b) Walters, M. A.; Shay, J. J. *Tetrahedron Lett.* **1995**, *36*, 575.

[15] Crystallographic data for **9b** have been deposited at the Cambridge Crystallographic Data Center (CCDC 913517).

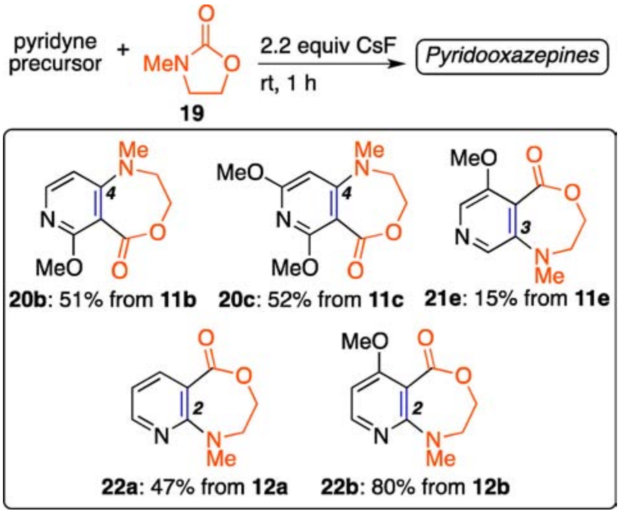
Scheme 5. Reaction of 3,4- and 2,3-Pyridynes and DMPU



initial nucleophilic addition of a nitrogen atom of DMPU to pyridyne. The reaction of 2,3-pyridyne generated from **12b** and DMPU also proceeded smoothly to give the coupling product **18** in 50% yield as a single regioisomer.

Finally, 1-methyl-2-oxazolidone (**19**) was employed for the coupling reactions with pyridynes (Scheme 6). The reactions of 3,4-pyridyne precursors **11b** and **11c** and **19** gave the corresponding pyridooxazepine derivatives **20b** and **20c**, respectively, in moderate yields in a regioselective manner.[17] The reaction of 3,4-pyridyne having a 5-methoxy group with **19** also proceeded, but the yield of the product **21e** was lower. 2,3-Pyridynes were also applicable to the coupling reaction with **19**, and the pyridooxazepine derivatives **22a** and **22b** were obtained in moderate to good yields.

Scheme 6. Synthesis of Pyridooxazepines by the Coupling of Pyridynes and 1-Methyl-2-oxazolidone



In summary, we succeeded in the development of a new protocol for the synthesis of pyridodiazepines, pyridodiazocines, and pyridooxazepines by the reaction of 3,4-pyridynes and 2,3-pyridynes with cyclic ureas and 1-mehtyl-2-oxazolidone. It was also found that the regioselectivity of this reaction was strongly affected by the substituents on the pyridine ring. Further studies including evaluation of biological activities of the products synthesized by this protocol are in progress.[18]

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Supporting Information Available. Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For examples of pyridodiazocine synthesis, see: (a) van Otterlo, W. A. L.; Morgans, G. L.; Khanye, S. D.; Aderibigbe, B. A. A.; Michael, J. P.; Billing, D. G. *Tetrahedron Lett*. **2004**, *45*, 9171. (b) Tamura, Y.; Tsunekawa, M.; Ikeda, H.; Ikeda, M. *Heterocycles* **1982**, *19*, 1596. See also ref 7j.

(17) For examples of pyridooxazepine synthesis, see: (a) Adhikary, N. D.; Chattopadhyay, P. *Eur. J. Org. Chem*. **2011**, 7346. (b) Mc Gee, M. M.; Gemma, S.; Butini, S.; Ramunno, A.; Zisterer, D. M.; Fattorusso, C.; Catalanotti, B.; Kukreja, G.; Fiorini, I.; Pisano, C.; Cucco, C.; Novellino, E.; Nacci, V.; Williams, D. C.; Campiani, G. *J. Med. Chem*. **2005**, *48*, 4367. (c) Liegeois, J. F. F.; Rogister, F. A.; Bruhwyler, J.; Damas, J.; Nguyen, T. P.; Inarejos, M. O.; Chleide, E. M. G.; Mercier, M. G. A.; Delarge, J. E. *J. Med. Chem*. **1994**, *37*, 519. (d) Sleevi, M. C.; Cale, A. D., Jr.; Gero, T. W.; Jaques, L. W.; Welstead, W. J.; Johnson, A. F.; Kilpatrick, B. F.; Demian, I.; Nolan, J. C.; Jenkins, H. *J. Med. Chem*. **1991**, *34*, 1314. (e) Cale, A. D., Jr.; Gero, T. W.; Walker, K. R.; Lo, Y. S.; Welstead, W. J., Jr.; Jaques, L. W.; Johnson, A. F.; Leonard, C. A.; Nolan, J. C.; Johnson, D. N. *J. Med. Chem*. **1989**, *32*, 2178. (d) Schultz, A. G.; Flood, L.; Springer, J. P. *J. Org. Chem*. **1986**, *51*, 838.

(18) As a result of a preliminary investigation of the biological activity of pyridodiazepines, it was found that compound **7a** showed weak binding affinity to the benzodiazepine receptor.

The authors declare no competing financial interest.