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Synthesis of pyrrolo[1,3]diazepines by a dipolar cycloaddition – *retro*-Mannich domino reaction

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Abstract

Microwave irradiation facilitated the synthesis of 4-arylthio-3-oxazolin-5-ones from ethyl cyanoformate, thiophenol, and cyclic ketones. Subsequent decarboxylation and *in situ* [3+2] cycloaddition provided novel 2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepine scaffolds after a spontaneous *retro*-Mannich domino reaction.

The utility of 1,4-benzodiazepines in drug discovery has been extraordinary due to the remarkable therapeutic value of this class of azaheterocyclic compounds.² Benzodiazepine derivatives have been found to possess anticonvulsant to anxiolytic activities, and strong antitumor properties. Among other pharmacological functions, the much less broadly studied 1,3-diazepine derivatives have been of interest due to their inhibitory effects on HIV-1 protease, adenosine deaminase, and guanase, as well as their NK1 receptor binding properties (Fig. 1).³⁻⁴ However, there is still a relative dearth of synthetic methods to access fused 1,3-diazepine scaffolds, in particular the novel pyrrolo[1,3]diazepines.⁵ We have discovered an elegant domino reaction which readily converts 1,3-oxazolin-5-ones into pyrrolo[1,3]diazepines through a mechanistically intriguing cycloreversion, 1,3-dipolar cycloaddition, *retro*-Mannich reaction, and iminium ion addition sequence.

In this Letter, we describe a microwave accelerated synthesis of 4-arylthio-3-oxazolin-5-ones as well their *in situ* conversion to pyrrolo[1,3]diazepines and the further functionalization of these heterocyclic scaffolds.

In an earlier approach, one of us had synthesized 4-arylthio-3-oxazolin-5-ones in a ‘one-pot reaction’ from ethyl cyanoformate, thiophenol, and carbonyl compounds in the presence of diethylamine, BF₃-etherate, and titanium tetrachloride.⁶ In an analogous sequence, but using microwave heating in a monomode reactor, we synthesized the piperidyl 3-oxazolin-5-one **4** from 1-benzylpiperidin-3-one **3** (Scheme 1). Significantly, the oxazolinone formation was thus expedited from a 12–36 h reaction time⁶ to 15 min at 80 °C under microwave irradiation, and the yield was increased to 60%.

Heating 0.5 M solution of **4** in chlorobenzene at 150 °C for 10 min in the microwave reactor released carbon dioxide to generate the intermediate nitrile ylide **I**₁,⁷ which was spontaneously trapped by the powerful dipolarophile dimethyl acetylenedicarboxylate (DMAD) in a 1,3-dipolar cycloaddition reaction (Scheme 2).^{7,8} However, rather than the expected spirocycle **I**₂, the pyrrolo[1,3]diazepine **5** was isolated in good yield as the end product of a spontaneous

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retro-Mannich-aminal formation pathway which likely includes the zwitterionic **I**₃ as yet another step along a largely unprecedented cascade process.

Intrigued by this domino process⁹ as well as the opportunity for ready access to unusual pyrrolo [1,3]-diazepine derivatives, we evaluated its scope with electron-deficient alkynes (Table 1). In all cases, generation of the thio-substituted nitrile ylide was achieved by microwave mediated thermolysis of the oxazolinone **4** in chlorobenzene at 150 °C for 10 min. Reactive electron-deficient alkyne dipolarophiles such as DMAD (Entry 1) and methyl propiolate (Entry 2) gave high to moderate yields of the cascade products **5** and **6** (77% and 47%, respectively). Interestingly, the 1,3-dipolar cycloaddition of nitrile ylide **I**₁ with methyl propiolate proceeded regiospecifically to give diazepine **6** as a single detectable product, assigned by 2D NOESY analysis. The observed regioselectivity in the cycloaddition suggests that the ylide carbon in **I**₁ is more nucleophilic than the nitrile carbon, attacking the monosubstituted alkyne at the more electrophilic β-carbon. This regioselectivity is in contrast to the cycloaddition of related nitrile ylides to carbonyl compounds.⁷ It is also noteworthy that a previous attempt for the 1,3-dipolar cycloaddition of the cyclohexyl analog of oxazolinone **4** to ethyl propiolate failed, leading instead to a [1,4]H shift in the ylide to give an aza-1,3-butadiene intermediate, followed by the formation of a tetrahydroquinoline by way of a Diels-Alder reaction with the propiolate.⁷ A possible explanation for this difference in reactivity is that the presence of the nitrogen atom in the ylide carbon substituent inductively activates the ylide, or disfavors the [1,4]H shift sufficiently to allow a dipolar addition to the less reactive (compared to DMAD) propiolate.

In support of an unusually high reactivity of the piperidyl nitrile ylide **I**₁, even the use of 2-ethynylpyridine led to dipolar cycloaddition products, albeit in a rather low overall yield of 34% (Entry 3). The regioisomers **7a** and **7b** were isolated as an inseparable 1.7:1 mixture. Methyl phenylpropiolate resulted in a 1.6:1 mixture of regioisomeric adducts **8a** and **8b** in a combined yield of 11% (Entry 4). Similarly, methyl but-2-ynoate derived pyrrolo[1,3]-diazepines **9a** and **9b** were also obtained as an inseparable mixture of regioisomers (Entry 5). In the latter three reactions, the structure of the major regioisomer was not assigned. Due to an extensive thermal alkyne decomposition observed by ¹H NMR analysis of the crude reaction mixture, methyl 3-(pyridin-2-yl)propiolate did not provide any desired product (Entry 6). Accordingly, while the opportunity for synthesizing pyrrolodiazepine derivatives **5-9** in two steps remains intriguing, the reaction scope is still limited to moderately to highly activated, thermally stable dipolarophiles. We intend to develop catalytic, less harsh reaction conditions in order to expand the scope of this novel transformation to more temperature-sensitive alkynes. In contrast, we were able to showcase the possibility for further ring conversions of pyrrolodiazepines **5-9** in the efficient generation of an azamacrocyclic scaffold (Scheme 3).¹⁰

While the aminal function in the pyrrolo[1,3]diazepine **5** is sufficiently resistant to hydrolysis to allow biological assays under standard conditions, cleavage can be accomplished in a 5:1 mixture of AcOH and H₂O for 2 d at 90 °C. The benzylic amine **10** was isolated in 85% yield. Subsequent selective *N*-amidation was affected by acyl transfer with *in situ* prepared imidazolium salt **11**.¹¹ The resulting urea **12** was *N*-allylated in the presence of a five-fold excess of allyl bromide and K₂CO₃ in dioxane at reflux to give diene **13**.¹² Ring closing metathesis with ruthenium catalyst **14**¹³ under a nitrogen atmosphere gave the 12-membered macrocycle **15** in good yield as a 3:1 mixture of (*Z/E*)-isomers.

The formation of a mixture of *cis/trans*-isomers in the RCM preparation of a macrocycle is not unexpected.^{13,14} We performed conformational minimizations of the structures of *cis*- and *trans*-**15** using Spartan 08 with the MMFF parameterization and found the putative global minima to have essentially identical steric energies. *Cis*-**15** displayed a half-boat-conformation of the 12-membered ring, whereas *trans*-**15** showed a crown-like, more rectangular

conformation (Figure 2). In both cases, the macrocycle minimized the nonbonding interactions of the urea substituents.

In conclusion, we were able to apply new microwave heating conditions to the synthesis of 4-arylthio-3-oxazolin-5-one **4**. Thermolysis of this spirocycle revealed a mechanistically unique domino reaction, whereby expulsion of CO₂ led to a nitrile ylide which underwent *in situ* trapping with a 1,3-dipolarophile followed by a *retro*-Mannich reaction and iminium ion cyclization, terminating in the preparation of a pyrrolo[1,3]diazepine. Hydrolysis of the aminal function, and a sequence of *N*-carbamoylation, *N*-allylation, and RCM, provided access to 12-membered pyrrole-fused urea **15**. Pyrrole-containing natural products are known for attractive biological properties,¹⁵ and this work provides a new access to a diverse set of fused pyrrole derivatives.^{16–18}

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References

1. Present address: Laboratorio de Química Farmacéutica, DQO, Facultad de Química, Universidad de la República, Gral Flores 2124, CC 1157, Montevideo, Uruguay.
2. See, for example: Costantino L, Barlocco D. *Curr Med Chem* 2006;13:65–85. [PubMed: 16457640]
3. Dieltiens N, Claeys DD, Allaert B, Verpoort F, Stevens CV. *Chem Commun* 2005:4477–4478.
4. (a) Wang L, Hosmane RS. *Bioorg Med Chem Lett* 2001;11:2893–2896. [PubMed: 11677121] (b) Boks GJ, Tollenaere JP, Kroon J. *Bioorg Med Chem* 1997;5:535–547. [PubMed: 9113332]
5. The synthesis and biology of pyrrolo[1,3]diazepines remain essentially unexplored, in spite of some previous preparative work: (a) Daich A, Ohier P, Decroix B. *J Heterocyclic Chem* 1995;32:1731–1734. (b) El-Kashef H, Rathelot P, Vanelle P, Rault S. *Monatshefte Chem* 2007;138:469–476. (c) Mahaffey RL, Atwood JL, Humphrey MB, Paudler WW. *J Org Chem* 1976;41:2963–2965.
6. (a) Wipf P, Heimgartner H. *Tetrahedron Lett* 1984;25:5127–5128. (b) Wipf P, Prewer R, Bieri JH, Heimgartner H, Nastopoulos V, Germain G. *Helv Chim Acta* 1987;70:1380–1388.
7. (a) Wipf P, Heimgartner H. *Chimia* 1984;38:357–359. (b) Wipf P, Prewer R, Bieri JH, Germain G, Heimgartner H. *Helv Chim Acta* 1988;71:1177–1190.
8. Sharp, JT. “Nitrile ylides and nitrile imines.” In “Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products”. In: Padwa, A.; Pearson, WH., editors. *Chem Heterocycl Compds*. Vol. 59. 2002. p. 473–538.
9. Tietze LF, Modi A. *Med Res Rev* 2000;20:304–322. [PubMed: 10861729]
10. For the use of azamacrocycles in diversity-oriented synthesis, see, for example: (a) Wipf P, Stephenson CRJ, Walczak MAA. *Org Lett* 2004;6:3009–3012. [PubMed: 15330670] (b) Wessjohann LA, Ruijter E. *Top Curr Chem* 2005;243:137–184.
11. Grzyb JA, Shen M, Yoshina-Ishii C, Chi W, Brown S, Batey RA. *Tetrahedron* 2005;71:153–1715.
12. Albano V, Gualandi A, Monari M, Savoia D. *J Org Chem* 2008;73:8376–8381. [PubMed: 18826281]
13. Lee CW, Grubbs RH. *J Org Chem* 2001;66:7155–7158. [PubMed: 11597245]
14. (a) Hansen EC, Lee D. *J Am Chem Soc* 2004;126:15074–15080. [PubMed: 15548004] (b) Kaul R, Surprenant S, Lubell WD. *J Org Chem* 2005;70:3838–3844. [PubMed: 15876068]
15. See: Jin Z. *Nat Prod Rep* 2009;26:382–445. [PubMed: 19240947], and references cited therein.
16. Experimental protocol and spectral data of **4**: **1-Benzyl-3-piperidone**. A solution of K₂CO₃ (0.546 g, 2.63 mmol) in deionized water (5.0 mL) was added at rt to 1-benzyl-3-piperidone hydrochloride hydrate (0.600 g, 2.63 mmol). The reaction mixture was stirred for 90 min and extracted into ethyl acetate. The organic layer was dried (MgSO₄), filtered, and concentrated to obtain 1-benzyl-3-piperidone (free-base) as a viscous brown-oil (0.492 g, 2.60 mmol, 99%) upon drying under high-vacuum for 1 h. **7-Benzyl-3-(phenylthio)-1-oxa-4,7-diazaspiro[4.5]dec-3-en-2-one (4)**. To a

microwave vial containing a solution of thiophenol (0.0689 g, 0.625 mmol) in dry dichloromethane (0.98 mL) was added ethyl cyanoformate (0.0503 g, 0.507 mmol) and Et₂NH (1 drop) at 0 °C. The reaction mixture was stirred under an atmosphere of N₂ at rt for 2 h. At 0 °C, 0.5 mL of a freshly-prepared catalyst stock solution (TiCl₄ (20 drops) and BF₃·Et₂O (10 drops of) in dichloromethane (3.0 mL) mixed under N₂ at rt) was added dropwise, followed by addition of 1-benzyl-3-piperidone (0.0935 g, 0.516 mmol). The reaction mixture was heated in the microwave at 80 °C for 15 min and diluted with EtOAc and 5 M NaOH (1.0 mL). The aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. The crude residue was purified by chromatography on SiO₂ (88% hexanes/EtOAc) to yield **4** (0.106 g, 0.301 mmol, 60%) as a light yellow-orange viscous oil. Upon refrigeration, **4** turned into an amorphous wax after several days: IR 2946, 2928, 2805, 2788, 2764, 1770, 1577, 1560, 1439, 1299, 1251, 1114, 1053, 1027, 975, 917, 900, 738, 701, 684 cm⁻¹; ¹H NMR (CDCl₃, 300 K) δ 7.57-7.54 (m, 2 H), 7.41-7.39 (m, 3 H), 7.27-7.19 (m, 5 H), 3.60, 3.51 (AB, 2 H, *J* = 13.5 Hz), 2.82 (dt, 1 H, *J* = 11.1, 3.6 Hz), 2.51 (s, 2 H), 2.20 (app t, 1 H, *J* = 10.5 Hz), 2.01-1.57 (m, 4 H); ¹³C NMR (CDCl₃, 300 K) δ 162.7, 161.5, 137.7, 133.9, 129.9, 129.5, 128.8, 128.4, 127.2, 126.4, 106.8, 62.0, 59.8, 52.1, 34.3, 22.1; TOFMS *m/z* 375 ([M+Na]⁺, 10), 365 (30), 353 ([M+H]⁺, 100); HRMS (ES) *m/z* calcd for C₂₀H₂₀N₂O₂SNa (M+Na) 375.1143, found 375.1114.

17. Experimental protocol and spectral data of **dimethyl 2-benzyl-8-(phenylthio)-2,3,4,5-tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]diazepine-6,7-dicarboxylate (5)**. A solution of acetylenecarboxylic acid dimethyl ester (0.0745 g, 0.504 mmol) in chlorobenzene (0.5 mL) was treated with **4** (0.0888 g, 0.252 mmol). The reaction mixture was stirred at 150 °C for 10 min under microwave irradiation (200 W). Without removal of the chlorobenzene, the crude reaction mixture was purified by chromatography on SiO₂ (eluting with 100% to 80% hexanes/EtOAc). The residue was further purified by Kugelrohr distillation (0.1 Torr, 100 °C) to yield **5** (0.0879 g, 0.195 mmol, 77%) as a light yellow oil which turned into a yellow-orange glass upon further drying under high-vacuum and extended refrigeration: IR 2945, 1705, 1495, 1439, 1273, 1204, 1178, 1128, 1049, 1027, 738, 697 cm⁻¹; ¹H NMR (CDCl₃, 295 K) δ 7.32-7.18 (m, 8 H), 7.13-7.06 (m, 2 H), 5.13 (bs, 2 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.39 (s, 2 H), 3.40-3.20 (bm, 2 H), 3.01 (dd, 2 H, *J* = 4.8, 5.1 Hz), 1.72-1.62 (m, 2 H); ¹³C NMR (CDCl₃, 300 K) δ 166.2, 164.7, 143.7, 138.0, 136.4, 129.3, 128.5, 127.4, 126.4, 125.4, 120.0, 111.5, 65.6, 54.6, 52.8, 52.4, 51.6, 25.6, 22.2; TOFMS *m/z* 474 (3), 473 ([M+Na]⁺, 100), 451 ([M+H]⁺, 3); HRMS (ES) *m/z* calcd for C₂₅H₂₆N₂O₄SNa (M+Na) 473.1502, found 473.1511.
18. Experimental protocol for RCM of **13** and spectral data of **dimethyl 4-benzyl-6-methyl-5-oxo-12-(phenylthio)-1,2,3,4,5,6,7,10-octahydropyrrolo[2,1-*g*][1,3,8]triazacyclododecine-13,14-dicarboxylate ((*Z*)-15)**. A solution of diene **13** (0.0180 g, 0.0313 mmol) in dry dichloromethane (7.0 mL) was treated with 2nd generation Grubbs catalyst **14** (0.00531 g, 0.00625 mmol), heated at reflux for 5 h, cooled to rt, filtered through a pad of celite/florisil (1:1), and washed with EtOAc. The eluent was concentrated, and the residue was purified by chromatography on SiO₂ (80% hexanes/EtOAc) to yield **15** as a colorless oil (0.0125 g, 0.0228 mmol, 73%) and a mixture of (*Z/E*)-isomers (3:1). Major (*Z*)-isomer: IR 2946, 1705, 1636, 1495, 1446, 1210, 1075, 1027, 732, 701 cm⁻¹; ¹H NMR (CDCl₃, 300 K) δ 7.36-7.14 (m, 10 H), 5.76 (dt, 1 H, *J* = 7.8, 10.8 Hz), 5.15 (dt, 1 H, *J* = 6.6, 10.8 Hz), 4.74 (d, 2 H, *J* = 6.0 Hz), 4.53 (bs, 2 H), 3.94 (bs, 2 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.24 (bs, 2 H), 2.93-2.87 (m, 2 H), 2.85 (s, 3 H), 1.70-1.60 (m, 2 H); ¹³C NMR (CDCl₃, 300 K) δ 166.2, 165.0, 163.8, 143.1, 137.8, 135.9, 133.8, 129.4, 129.1, 128.7, 127.7, 127.5, 127.3, 126.5, 125.4, 118.9, 111.5, 54.8, 52.4, 51.4, 47.0, 45.7, 42.1, 35.6, 29.7, 28.0, 22.9; MS (EI) *m/z* 547 (M⁺, 3.5), 424 (9), 91 (100); HRMS (EI) *m/z* calcd for C₃₀H₃₃N₃O₅S 547.2122, found 547.2141. Minor (*E*)-isomer: ¹H NMR (CDCl₃, 300 K) δ 7.35-7.11 (m, 10 H), 5.85 (dt, 1 H, *J* = 5.7, 15.5 Hz), 5.38 (dt, 1 H, *J* = 6.3, 15.5 Hz), 4.76 (d, 2 H, *J* = 5.7 Hz), 4.38 (s, 2 H), 3.86 (s, 3 H), 3.77 (s, 3 H), 3.68-3.65 (m, 2 H), 3.12 (bs, 2 H), 2.90-2.85 (m, 2 H), 2.82 (s, 3 H), 1.78-1.69 (m, 2 H).

Figure 1.
Representative examples of pharmaceutically relevant 1,3-diazepine derivatives.

Figure 2.
Ball-and-stick models of force-field minimized lowest-energy conformations of *cis*-**15** (left) and *trans*-**15** (right).

Scheme 1.

Microwave-mediated synthesis of piperidyl 4-arylthio-3-oxazolin-5-one **4** in the presence of diethylamine and Lewis acid catalysts.

Scheme 2.

Suggested mechanism for the domino process – 1,3-dipolar cycloaddition of the nitrile ylide **I**₁ derived from **4** to DMAD, *retro*-Mannich reaction, and imine addition – generating the pyrrolo[1,3]-diazepine **5**.

Scheme 3.

Conversion of pyrrolodiazepine **5** to the free amine **10** serves as an entry point for ring expansion to access the fused macrocyclic urea **15**.

Table 1

Domino reactions of **4** with 1,3-dipolarophiles under microwave heating conditions.

Entry	Alkyne	Product	R ₁	R ₂	Yield
5	$MeO_2C-C\equiv C-CO_2Me$	5	CO ₂ Me	CO ₂ Me	77%
6	$MeO_2C-C\equiv C-CO_2Me$	6	CO ₂ Me	H	47%

Entry	Alkyne	Product	R ₁	R ₂	Yield
7a		7a	2-Pyridyl	H	34%
7b		7b	H	2-Pyridyl

Entry	Alkyne	Product	R ₁	R ₂	Yield
4 ^a		8a	Phenyl	CO ₂ Me	11%
		8b	CO ₂ Me	Phenyl	
5 ^a		9a	CO ₂ Me	Me	20%
		9b	Me	CO ₂ Me	
6 ^b		-	-	-	-

^a Tetrahedron Lett. Author manuscript; available in PMC 2010 December 1.

^a Regioisomers were not separable by chromatography on SiO₂

^b No desired product was observed by ¹H NMR of the crude reaction mixture