ORGANIC LETTERS

2011
Vol. 13, No. 13
3289–3291

Enone–Alkyne Reductive Coupling: A Versatile Entry to Substituted Pyrroles

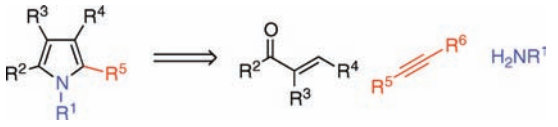
Benjamin B. Thompson and John Montgomery*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055, United States

jmontg@umich.edu

Received April 28, 2011

ABSTRACT



The reductive coupling of enones or enals with alkynes, followed by olefin oxidative cleavage and Paal–Knorr cyclization, provides a versatile entry to a variety of pyrrole frameworks. A number of limitations of alternate entries to the requisite 1,4-dicarbonyl intermediate are avoided. Classes of pyrroles that are accessible by this approach include 2,3-, 2,4-, 1,2,3-, 1,2,4-, 2,3,5-, and 1,2,3,5-substituted monocyclic pyrroles as well as a number of fused-ring polycyclic derivatives.

The pyrrole heterocycle is a key structural element in numerous natural products, synthetic medicinal agents, and novel materials.[1] In addition to strategies that functionalize an existing pyrrole ring, numerous cyclization and cycloaddition strategies for constructing complex pyrroles have been developed.[1,2] The Paal–Knorr condensation of 1,4-dicarbonyls with ammonia or primary amines is among the most versatile and widely used of the many strategies that have been developed.[3] The requisite 1,4-dicarbonyl precursor may be prepared from a linear precursor by oxidation state adjustments or alternatively, attractive entries via Stetter additions[4] or enolate heterodimerizations[5] have been developed in recent years (Scheme 1). While Stetter reactions and enolate heterodimerizations provide exceptionally versatile entries to 1,4-dicarbonyls, several notable limitations exist. For example, given the undesirable side reactions and self-condensations that occur with enals and formaldehyde in the Stetter reaction, aldehyde products are difficult to obtain, thus limiting access to pyrroles where R^2 or $R^5 = H$.[6] Similarly, enolate heterodimerizations that install hydrogen functionality at these positions are plagued by difficulties in avoiding homocoupling and in developing well-behaved aldehyde enolization processes.[7] Additionally, certain classes of polycyclic pyrroles are difficult to access by these methods given complexities in accessing the required 1,4-dicarbonyl substrates.

(1) (a) Fan, H.; Peng, J. N.; Hamann, M. T.; Hu, J. F. *Chem. Rev.* **2010**, *110*, 3850–3850. (b) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421. (c) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095–3110. (d) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213–7256.

(2) (a) St. Cyr, D. J.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366–12367. (b) Morin, M. S. T.; St-Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2010**, *12*, 4916–4919. (c) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62. (d) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074–2075. (e) Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Tseng, J. C.; Luh, T. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992–4993. (f) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 3941–3944. (g) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811–1813.

(3) (a) Knorr, L *Ber.* **1884**, *17*, 2863–2870. (b) Paal, C. *Ber.* **1884**, *17*, 2756–2767. (c) Braun, R. U.; Zeitler, K.; Muller, T. J. J. *Org. Lett.* **2001**, *3*, 3297–3300. (d) Braun, R. U.; Muller, T. J. *Synthesis* **2004**, 2391–2406. (e) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465–2468. (f) Werner, S.; Iyer, P. S.; Fodor, M. D.; Coleman, C. M.; Twining, L. A.; Mitasev, B.; Brummond, K. M. *J. Comb. Chem.* **2006**, *8*, 368–380. (g) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277–5288.

(4) (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–647. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (c) de Alaniz, J. R.; Rovis, T. *Synlett* **2009**, 1189–1207. (d) Nahm, M. R.; Linghu, X.; Potnick, J. R.; Yates, C. M.; White, P. S.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2377–2379. (e) Nahm, M. R.; Potnick, J. R.; White, P. S.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 2751–2756.

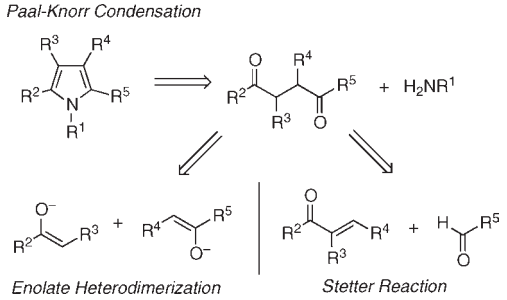
(5) (a) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083–7086. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560. (c) Clift, M. D.; Thomson, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 14579–14583. (d) Clift, M. D.; Taylor, C. N.; Thomson, R. J. *Org. Lett.* **2007**, *9*, 4667–4669.

(6) For alternate reactivity of enals under Stetter-type conditions, see: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370–14371. (b) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418–2439.

(7) For effective heterodimerizations involving aldehyde substrates, see: Jang, H. Y.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004–7005.

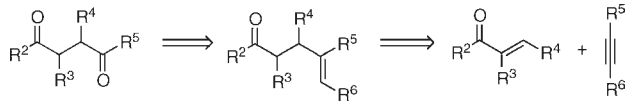
10.1021/ol201133n
Published on Web 06/09/2011

Scheme 1. Representative Entries to Substituted Pyrroles



Given these challenges, we were attracted to the oxidative cleavage of γ,δ-unsaturated carbonyls as an entry to 1, 4-dicarbonyl precursors for Paal–Knorr condensations. Extensive recent work from our laboratory has focused on developing entries to γ,δ-unsaturated carbonyls from nickel-catalyzed couplings and cyclizations of enones or enals with alkynes.[8,9] These advances allow hydrogen or non-hydrogen substituents at any of the positions R^2–R^5 (Scheme 2), and they provide access to a broad variety of linear or cyclic frameworks. These features provide considerable flexibility in the types of pyrroles that could be accessed by such a strategy. In this communication, we describe representative entries to various classes of pyrroles by this approach to illustrate the pyrrole structural variations that may be accessed.

Scheme 2. 1,4-Dicarbonyls from Enone–Alkyne Reductive Coupling/Oxidative Cleavage



Our studies began with an investigation of intermolecular reductive couplings of acyclic enones or enals with alkynes (Table 1). These substrate combinations provide the γ,δ-unsaturated carbonyls required for accessing monocyclic pyrroles **5** with varying substitution patterns at R^1, R^2, and R^5. As the examples below illustrate, the positions R^2 and R^5 adjacent to the pyrrole nitrogen are installed from the enone carbonyl substituent and from an alkyne substituent. These two positions may both be functionalized (Table 1, entries 1, 2, and 7), or alternatively, hydrogen substituents may be installed from either a terminal alkyne (Table 1, entries 3 and 4) or an enal (Table 1, entries 5 and 6) component. The pyrrole positions remote from nitrogen (R^3 and R^4) are most readily installed by utilizing a β-substituted enone or enal as each of the examples illustrate (shown here as an R^4 substituent). While hydrogen and aromatic functionality were the primary focus of this study, aliphatic groups may also be installed (entry 7). Standard Paal–Knorr protocols for condensation of either ammonium acetate or a primary amine under microwave conditions easily allow the R^1 position to be substituted or unsubstituted.[3] Using this simple combination of substrates (enone/enal, alkyne, and amine), a broad array of pyrrole substitution patterns are available by choice of the appropriate substitution pattern in each of the requisite substrates.

In addition to monocyclic pyrroles obtained by intermolecular reductive couplings, nickel-catalyzed cyclizations of alkynyl enones provides simple access to more structurally complex bicyclic and tricyclic pyrroles (Table 2). While reductive cyclizations directly analogous to the intermolecular couplings described above (Table 1) are possible, alkylative versions of the process are generally more efficient for intramolecular cases.[9] In the alkylative variant, $Ni(COD)_2$ alone is employed as a catalyst without ligand additives. Employing dimethylzinc as the reducing agent then transfers a methyl group to the substrate in the exocyclic position, in contrast to the delivery of a hydrogen substituent in the intermolecular, triethylborane protocol. Since the exocyclic substituents are oxidatively removed in the conversion to the pyrrole products, the exocyclic group is of no consequence in the synthesis of pyrroles.

In order to illustrate the general strategy, three intramolecular templates were chosen for study. In the first example (Table 2, entry 1), substrate **6a** was employed to provide cyclization adduct **7a** from dimethylzinc-promoted cyclization. Oxidative cleavage, followed by Paal–Knorr condensation with ammonium acetate, provided access to tricyclic product **9a**. Next, substrate **6b** with an all-carbon tether chain was employed to afford product **7b** after dimethylzinc-promoted cyclization. Oxidative cleavage and ammonium acetate condensation provided bicyclic pyrrole **9b** in high yield. Finally, oxazolidinone-derived substrate **6c** was employed in a dimethylzinc-promoted cyclization to afford adduct **7c**. Conversion of this structure to tricyclic product **9c** proceeded smoothly. The range of fused-ring carbocyclic and heterocyclic arrays prepared illustrates the variety of pyrrole derivatives that may be accessed by this approach.[10]

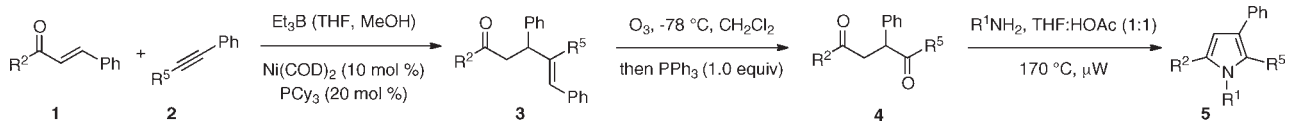
While the synthesis of pyrroles was our primary focus, the 1,4-dicarbonyl species utilized may be readily converted to the corresponding furans in a straightforward

(8) For reductive (H atom transfer) variants, see: (a) Herath, A.; Thompson, B. B.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712–8713. (b) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 8132–8133. (c) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469–471. (d) Li, W.; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17024–17029. (e) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696–9697. (f) Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032–12041.

(9) For alkylative (alkyl transfer) variants, see: (a) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099–2100. (b) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911–4920. (c) Montgomery, J.; Chevliakov, M. V.; Brielmann, H. L. *Tetrahedron* **1997**, *53*, 16449–16462. (d) Montgomery, J.; Seo, J.; Chui., H. M. P. *Tetrahedron Lett.* **1996**, *37*, 6839–6842. (e) Ni, Y.; Kassab, R. M.; Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17714–17718. (f) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (g) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015.

(10) For representative studies of fused ring pyrrole derivatives, see: (a) Jeannotte, G.; Lubell, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 14334–14335. (b) Jeannotte, G.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 4656–4662.

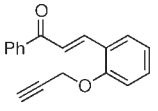
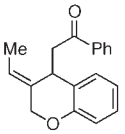
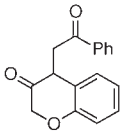
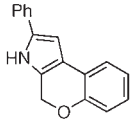
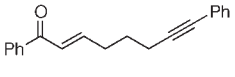
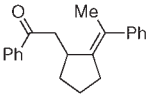
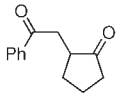
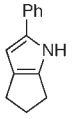
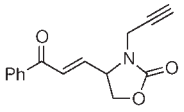
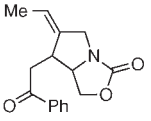
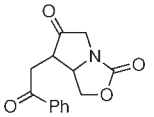
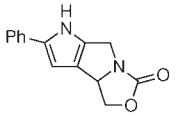
Table 1. Monocyclic Pyrroles from Intermolecular Reductive Couplings



1 2 3 4 5

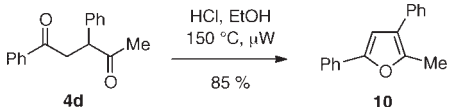
entry	R^1	R^2	R^5	yield (%) of **3**	yield (%) of **4**	yield (%) of **5**
1	H	Ph	Ph	81	94	97
2	*p*-tolyl	Ph	Ph	81	94	62
3	H	Ph	H	88	83	61
4	Ph	Ph	H	88	83	71
5	H	H	Ph	50	77	76
6	Ph	H	Ph	50	77	75
7	H	Ph	Me	92	64	99

Table 2. Bicyclic and Tricyclic Pyrroles from Intramolecular Alkylative Coupling

entry	substrate	alkylative cyclization[a]	oxidative cleavage[b]	Paal-Knorr condensation[c]
1	 **6a**	 **7a** (47 %)	 **8a** (62 %)	 **9a** (35 %)
2	 **6b**	 **7b** (45 %)	 **8b** (96 %)	 **9b** (92 %)
3	 **6c**	 **7c** (69 %)	 **8c** (62 %)	 **9c** (99 %)

[a] 10 mol % $Ni(COD)_2$, 1.5 equiv of Me_2Zn (2.0 M in toluene), 0.07 M THF, 0 °C. [b] (1) O_3, −78 °C, CH_2Cl_2; (2) 1 equiv of PPh_3, rt. [c] For product **9a**: 3 equiv of NH_4OAc, 2 equiv of TsOH, 4 Å MS, THF/EtOH (1:2), reflux. For products **9b** and **9c**: 4.5 equiv of NH_4OAc, 4 Å MS, THF/AcOH (1:1), 170 °C μW, 15 min.

fashion.[3g] As illustrated with compound **4d** (as prepared in Table 1, entry 7), acid-catalyzed condensation of the 1, 4-dicarbonyl species directly affords the corresponding furan **10** in good yield (eq 1).



4d **10** (1)

In summary, a versatile new entry to 1,4-dicarbonyl derivatives has been developed, involving nickel-catalyzed coupling or cyclization of enones or enals with alkynes followed by oxidative cleavage. Further functionalization by standard Paal−Knorr cyclizations provides rapid access to a variety of substituted pyrrole derivatives. Various substitution patterns may be accessed with monocyclic pyrroles, and a number of polycyclic derivatives with fused carbocyclic or heterocyclic rings are also accessible. A number of the classes of pyrroles that may be accessed by this method are difficult to access by alternate approaches, and the reductive coupling approach provides complementary characteristics to alternative procedures including enolate heterodimerizations and Stetter reactions.

Acknowledgment. Support for this work was provided by the National Science Foundation (CHE-1012270).

Supporting Information Available. Experimental procedures and copies of spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.