Studies towards a new one-pot heterocyclization: Bu^{t}OK-promoted oxa- and aza-Michael addition–intramolecular carbocyclization of prop-2-ynyl alcohols and amines with α,β-disubstituted nitroalkenes

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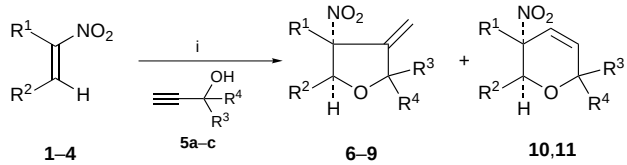
Bu^{t}OK-promoted reaction of prop-2-ynyl alcohols 5 or *N*-methylprop-2-ynylamine 12 with nitroalkenes 1–4 affords 3-methylenetetrahydrofurans 6–9 and 3,4-dihydropyrans 10 and 11 or 3-methylenepyrrolidines 13–16, respectively, in moderate to good yields, with total allylic 1,3-strain-controlled diastereoselectivity.

Five-membered heterocycles are among the most common structures in bioactive compounds.[1] Moreover, the presence of an unsaturated bond available for further elaboration, particularly in α-methylene γ-butyrolactones,[2] has for many years stimulated interest in synthetic routes to 3-methylenetetrahydrofurans.[2,3] Finally, the pyrrolidine ring is an extensively studied heterocyclic system,[4] as a consequence of the interesting biological activity exhibited by several polysubstituted pyrrolidines.[5] This paper describes a new one-pot access to these heterocyclic compounds from readily available α,β-disubstituted nitroalkenes **1**–**4**.

While the oxa-Michael addition of prop-2-ynyl alcohols to β-monosubstituted α-nitroalkenes in the presence of sodium or potassium hydride led to β-nitroprop-2-ynyl ethers,[6] to the best of our knowledge, only few recent preparation of five- or six-membered heterocycles involve intramolecular addition of carbon nucleophiles to alkynes;[7]† among them, Bu^{t}OK-promoted double Michael addition of 4-hydroxybut-2-ynoates[8] and tandem oxa-Michael S_N2' substitution of 4-chlorobut-2-yn-1-ol[9] with α,β-disubstituted nitroalkenes generate a nitro-stabilized carbon nucleophile, which adds to the activated alkyne moiety to provide unsaturated tetrahydrofurans or pyrans.‡ Also of interest is the two-step synthesis of α-methylene γ-lactams from 1-nitrocyclohexene, involving the formation of β-nitroamides, which then undergo a Triton B-promoted carbanion addition to an unactivated terminal alkyne.[10] These results enhance the crucial effect of both the nitroalkene substitution pattern and the nature of the base on the reaction process.

Therefore, we investigated the base-promoted Michael addition of prop-2-ynyl alcohols **5a**–**c** to α,β-disubstituted



1,**6**,**10** R^1–R^2 = –$(CH_2)_4$–
2,**7** R^1–R^2 = –$(CH_2)_3$–
3,**8**,**11** R^1 = Me, R^2 = C_5H_{11}
4,**9** R^1 = Me, R^2 = Ph

a R^3 = R^4 = H
b R^3 = H, R^4 = Me
c R^3 = R^4 = Me

Scheme 1

Table 1 Heterocyclization of nitroalkenes **1**–**4**

Nitroalkene	Prop-2-ynyl alcohol **5**	Yield (%)[a]	Products	Ratio 5-*exo*/6-*endo*
1	**a**	78	**6a** + **10a**	1.7 : 1
1	**b**	47	**6b** + **10b**	3 : 1
1	**c**	31	**6c** + **10c**	8 : 1
2	**a**	84	**7a**[b]	
2	**b**	80	**7b**[b]	
2	**c**	78	**7c**[b]	
3	**a**	57	**8a** + **11a**	20 : 1
3	**b**	20	**8b** + **11b**	10 : 1
3	**c**	25	**8c** + **11c**	16 : 1
4	**a**	73	**9a**[b]	
4	**b**	31	**9b**[b]	
4	**c**	58	**9c**[b]	

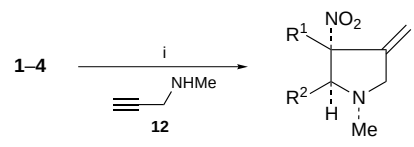
[a] Isolated total yields of chromatographically homogeneous, spectroscopically pure products are reported. [b] 6-*endo* adducts were not detected by ^{1}H NMR in the crude reaction mixture.

α-nitroalkenes **1**–**4**, since this route should afford 3-methylenetetrahydrofurans, provided a nucleophilic addition of the resulting nitronate on the triple bond occurs.

Best results were obtained when nitroalkenes **1**–**4** were added slowly to a solution of prop-2-ynyl alcohols **5** in THF containing Bu^{t}OK (Scheme 1). Other bases such as BuLi, KH, or K_2CO_3 were ineffective; for instance, the reaction of **1** with **5a** in the presence of BuLi produced a complex reaction mixture,§ while changing the base for KH delivered β-nitroprop-2-ynyl ethers.[6]

Although the reaction proceeded with total diastereoselectivity due to allylic 1,3-strain,[9,11] unexpected regioselectivity was observed (Table 1). Indeed, 5-*exo* adducts **6**–**9** were isolated, along with **10** and **11**¶‖ resulting from 6-*endo* cyclization mode when the reaction was performed on nitroalkenes **1** and **3** (ratio 5-*exo*/6-*endo* 1.7–20 : 1). Heterocycles **6b**–**9b** and **10b** and **11b** provided by reaction with secondary alcohol **5b** were obtained as a 0.7–0.9/1 mixture of diastereomers.

Interestingly, aza-Michael addition of *N*-methylprop-2-ynylamine **12** on nitroalkenes **1**–**4** also proceeded with intramolecular nucleophilic addition to provide, regio- and diastereo-selectively, 3-methylenepyrrolidines **13**–**16**¶‖ (Scheme 2).



Scheme 2

Factors that govern the regioselectivity of this new one-pot heterocyclisation are currently under investigation.

Footnotes and References

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† To the best of our knowledge, the construction of carbocycles by either intramolecular addition of alkyllithiums to non-terminal alkynes (ref. 12) or Pd-mediated cyclization of acetylenic compounds bearing a nucleophilic functionality (ref. 13) have never been extended to heterocycles.

‡ For other related intramolecular additions of stabilized carbon nucleophiles to activated alkynes, see ref. 14.

§ Prop-2-ynyloxycyclohexanone, resulting from Nef reaction of the β-nitroprop-2-ynyl ether intermediate, could be isolated from the reaction mixture (20% yield).

¶ Bicyclic adducts are *cis* ring fused.

‖ Satisfactory analytical and spectral data were obtained for all compounds. *Selected data* for **6a**: δ_H (400 MHz, $CDCl_3$) 1.45 (m, 3 H), 1.6 (m 2 H), 1.85 (m, 1 H), 2.15 (m, 1 H), 2.4 (m, 1 H), 4.45 (dt, *J* 13.6, 2.1, 1 H), 4.52 (dt, *J* 13.6, 2.6, 1 H), 4.54 (t, *J* 5.8, 1 H), 5.25 (td, *J* 2.1, 1.1, 1 H), 5.35 (td, *J* 2.6, 1.1, 1 H); δ_C (100.61 MHz, $CDCl_3$) 145.2, 109.5, 94.5, 80.0, 69.1, 31.2, 26.8, 21.8, 20.8. For **10a**: δ_H (400 MHz, $CDCl_3$) 1.45 (m, 3 H), 1.6 (m, 2 H), 1.85 (m, 1 H), 2.0 (m, 1 H), 2.3 (m, 1 H), 4.17 (dt, *J* 18.4, 2.6, 1 H), 4.22 (dt, *J* 18.4, 2.4, 1 H), 4.41 (dd, *J* 6.5, 4.7, 1 H), 5.84 (dt, *J* 10.2, 2.3, 1 H), 6.00 (dt, *J* 10.2, 2.5, 1 H); δ_C (100.61 MHz, $CDCl_3$) 131.0, 125.3, 88.2, 72.6, 63.3, 34.6, 26.9, 21.5, 21.2. For **13**: δ_H (400 MHz, $CDCl_3$) 1.75–1.27 (m, 6 H), 2.04–1.89 (m, 1 H), 2.28 (s, 3 H), 2.51–2.40 (m, 1 H), 3.17 (dt, *J* 13.9, 2.8, 1 H), 3.29 (m, 1 H), 3.59 (d, *J* 13.9, 1 H), 5.06 (ddd, *J* 2.3, 1.8, 0.5, 1 H), 5.19 (ddd, *J* 2.8, 2.1, 0.5, 1 H); δ_C (100.61 MHz, $CDCl_3$) 146.4, 107.9, 94.4, 66.8, 59.2, 39.1, 33.1, 22.3 (2C), 19.7; ν_{max}/cm^{-1} 2958, 1669, 1536, 1090, 1019, 798; *m*/*z* 196 (M^+, 12%), 163 (58), 150 (63), 149 (100), 148 (35).

1 M. H. D. Postema, *Tetrahedron*, 1992, **48**, 8545; W. Westle, *Polyether Antibiotics: Naturally Occuring Acid Ionophores*, Marcel Dekker, New York, 1982, vols. 1 and 2; T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309; A. Padwa, H. Nimmesgern and G. S. K. Wong, *J. Org. Chem.*, 1985, **50**, 5620.

2 M. Okabe, M. Abe and M. Tada, *J. Org. Chem.*, 1982, **47**, 1775; J.-P. Dulcère, M. N. Mihoubi and J. Rodriguez, *J. Org. Chem.*, 1993, **58**, 5709.

3 B. M. Trost and P. J. Bonk, *J. Am. Chem. Soc.*, 1985, **107**, 1778; J. Van der Louw, J. L. Van der Baan, H. Stichter, G. J. J. Out, F. J. J. de Kanter, F. Bickelhaupt and G. W. Klumpp, *Tetrahedron*, 1992, **48**, 9877; G. Pandey, K. S. S. Poleswara Rao and K. V. Nageshwar Rao, *J. Org. Chem.*, 1996, **61**, 6799; L. Engman and V. Gupta, *J. Org. Chem.*, 1997, **62**, 157; A. Krief and W. Dumont, *Tetrahedron Lett.*, 1997, **38**, 657.

4 J. Steele, *Contemp. Org. Synth.*, 1994, **1**, 95; M. Mori, N. Uesaka, F. Saitoh and M. Shibasaki, *J. Org. Chem.*, 1994, **59**, 5643.

5 A. R. Pinder, in *The Alkaloids*, ed. M. F. Grundon, Chemical Society, London, 1982, vol. 12.

6 J. L. Duffy, J. A. Kurth and M. J. Kurth, *Tetrahedron Lett.*, 1993, **34**, 1259.

7 M. Yoshimatsu, K. Machida, T. Fuseya, H. Shimizu and T. Kataoka, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1839.

8 T. Yakura, T. Tsuda, Y. Matsumura, S. Yamada and M. Ikeda, *Synlett*, 1996, 985.

9 J.-P. Dulcère and E. Dumez, *Chem. Commun.*, 1997, 971.

10 R. Patra, S. B. Maiti and A. Chatterjee, *Tetrahedron Lett.*, 1991, **32**, 1363.

11 R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.

12 W. F. Bailey, T. V. Ovaska and T. K. Leipert, *Tetrahedron Lett.*, 1989, **30**, 3901; W. F. Bailey and T. V. Ovaska, *Tetrahedron Lett.*, 1990, **31**, 627; G. Wu, F. E. Cederbaum and E. Negishi, *Tetrahedron Lett.*, 1990, **31**, 493; W. F. Bailey and T. V. Ovaska, *J. Am. Chem. Soc.*, 1993, **115**, 3080; W. F. Bailey and P. H. Aspris, *J. Org. Chem.*, 1995, **60**, 754; T. V. Ovaska, R. R. Warren, C. E. Lewis, N. Wachter-Jurcsak and W. F. Bailey, *J. Org. Chem.*, 1994, **59**, 5868.

13 G. Fournet, G. Balme and J. Goré, *Tetrahedron*, 1991, **47**, 6293.

14 S. H. Rosenberg and H. Rapoport, *J. Org. Chem.*, 1985, **50**, 3979; J. F. Lavallée, G. Berthiaume and P. Deslongchamps, *Tetrahedron Lett.*, 1986, **27**, 5455; E. J. Corey and W. Su, *Tetrahedron Lett.*, 1988, **29**, 3423; W. D. Rudorf and R. Schwartz, *Z. Chem.*, 1988, **28**, 101.

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