HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 901 - 906. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 27th August, 2014, Accepted, 10th September, 2014, Published online, 19th September, 2014
DOI: 10.3987/COM-14-S(K)109

SYNTHESIS AND STRUCTURAL ANALYSIS OF NINE-MEMBERED ENYNE NITROGEN HETEROCYCLES

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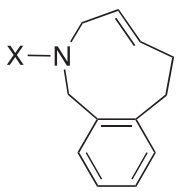
Abstract – An efficient approach to the nine-membered enyne nitrogen heterocycle **3** is presented. ^{1}H NMR analysis reveals that both **3a** (R = H, X = Ts) and **3b** (R = Me, X = Ts) exhibit significant labile planar chirality in solution at ambient temperature. The X-ray analysis of **3b** shows that the enantiotopic faces of the alkene are differentiated by the alkyne moiety in the solid state.

Medium-sized heterocycles containing unsaturated carbon-carbon bonds have attracted significant interest among both synthetic and structural organic chemists because of their unique conformational and chemical properties, made possible by the deformation and strain in their unsaturated carbon-carbon bonds.[1] Recently, we reported the novel 3-aza-5-[7]orthocyclophene **1**, containing a deformed (*E*)-alkene in the ansa chain, that showed stable planar chirality along with unique alkene reactivity owing to its strained cyclic structure.[2] We later reported the synthesis and stereochemical analysis of the cyclophyne analogue **2**, containing an alkyne instead of the (*E*)-alkene of **1**.[3] Cyclophyne **2** was found to possess significant labile planar chirality at ambient temperature.



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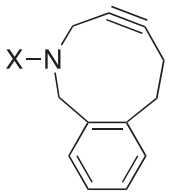

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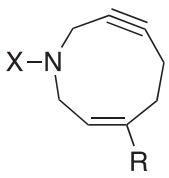
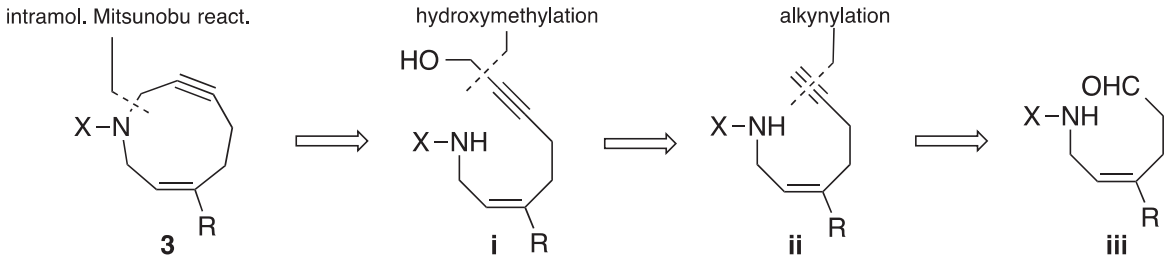


3

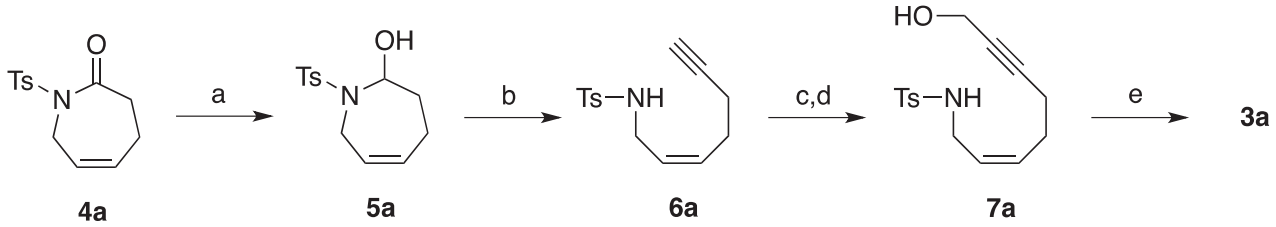
Dedicated with respect to Dr. Isao Kuwajima on the occasion of his 77th birthday

In connection with our research on the chemistry of medium-sized nitrogen heterocycles,[4] we became interested in the novel nine-membered enyne cyclic sulfonamide **3** (X = Ts), a congener of **2** containing a (*Z*)-alkene instead of a benzene ring. Herein, we report the synthesis and stereochemical analysis of **3**. Scheme 1 depicts the retrosynthetic strategy. We planned to construct the strained nine-membered skeleton of **3** by C–N bond formation via the intramolecular Mitsunobu reaction of **i**,[5,6] which can be prepared by the Seyferth-Gilbert alkynylation of aldehyde **iii** or its equivalent using the Ohira-Bestmann reagent,[7] followed by hydroxymethylation.



Scheme 1. Retrosynthetic analysis of **3**

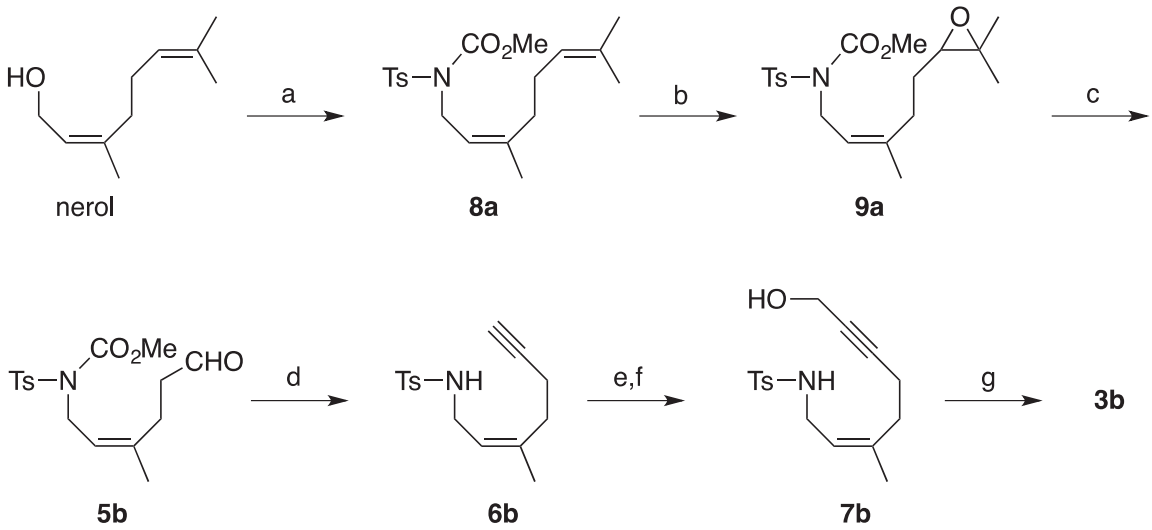
The synthesis of **3a** (R = H) began from our previously reported ε-lactam **4a** (Scheme 2).[4b] DIBAL reduction of **4a** gave hemiaminal **5a**, a tautomer of aldehyde **iii** (R = H, X = Ts). The reaction of **5a** with the Ohira-Bestmann reagent afforded enyne **6a** in 90% yield (two steps from **4a**). Hydroxymethylation of the terminal alkyne in **6a** was performed by an acylation and reduction sequence in 74% yield over two steps. The resulting **7a** was subjected to an intramolecular Mitsunobu reaction; treating **7a** with DEAD and PPh_3 in THF at 0 °C to rt under high-dilution conditions (0.01 M) successfully provided the desired cyclic enyne amide **3a** in good yield (80%).[8]



Scheme 2. Reagents and conditions: (a) DIBAL, CH_2Cl_2, –78 °C; (b) $MeCOC(N_2)PO(OMe)_2$, K_2CO_3, MeOH, rt, 90% (2 steps); (c) *n*-BuLi, THF, –78 °C, then $ClCO_2Me$, –78 °C → rt, 85%; (d) DIBAL, CH_2Cl_2, –78 °C, 87%; (e) DEAD, PPh_3, THF, 0 °C → rt, 80%.

The intramolecular Mitsunobu reaction approach was also applicable to the synthesis of methyl-substituted analogue **3b** (R = Me) (Scheme 3). The requisite key intermediate aldehyde **5b** [≡ **iii** (R = Me, X = Ts)] was prepared from nerol in three steps: (i) Mitsunobu reaction with methyl

N-(*p*-toluenesulfonyl)carbamate (93%), (ii) group-selective epoxidation of the trisubstituted alkene moiety with *m*CPBA (96%), and (iii) oxidative cleavage of the epoxide with orthoperiodic acid (97%). Similarly to the synthesis of **7a** from **5a**, alkynylation of **5b** followed by hydroxymethylation provided **7b**, albeit in moderate chemical yield. The intramolecular Mitsunobu reaction of **7b** proceeded smoothly and provided cyclic enyne sulfonamide **3b** in excellent yield (91%).[9] These results clearly show the efficiency of C–N bond formation by the Mitsunobu reaction in the construction of the strained cyclic skeletons of these nitrogen heterocycles.



Scheme 3. Reagents and conditions: (a) MeOCONHTs, DEAD, PPh_3, THF, 0 °C, 93%; (b) *m*CPBA, CH_2Cl_2, –78 → 0 °C, 96%; (c) H_5IO_6, Et_2O, 0 °C, 97%; (d) $MeCOC(N_2)PO(OMe)_2$, K_2CO_3, MeOH, rt, 44%; (e) *n*-BuLi, THF, –78 °C, then $ClCO_2Me$, –78 °C, 64%; (f) DIBAL, CH_2Cl_2, –78 °C, 84%; (g) DEAD, PPh_3, THF, 0 °C, 91%.

Sulfonamide **3b** afforded a crystal suitable for X-ray analysis, which revealed that the alkyne moiety is located on the outside of the plane of the alkene.[10] Hence, the enantiotopic faces of the alkene are differentiated (Figure 1), and **3b** possesses planar chirality in the solid state.

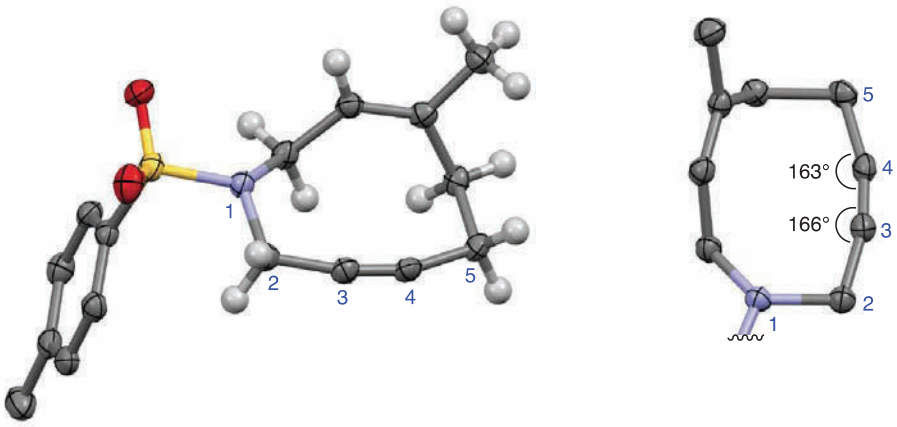


Figure 1. ORTEP drawing of **3b** (ellipsoid set at 40% of probability level)

Moreover, the alkyne moiety is significantly bent, with C2–C3–C4 and C3–C4–C5 bond angles of 166° and 163°, respectively.

The ^{1}H NMR spectrum of **3a** in $CDCl_3$ at ambient temperature showed a single set of geminal methylene protons alpha to the nitrogen atom. In contrast, a similar analysis of **3b** showed two sets of nonequivalent geminal methylene protons alpha to the nitrogen atom, suggesting that the aforementioned chiral conformations are maintained to some extent, even in solution and on the NMR time scale. The activation free energy for the racemization of **3a** and **3b** were estimated by DFT calculations as $\Delta G^{\ddagger}$ = 9.9 kcal mol^{-1}, and $\Delta G^{\ddagger}$ = 12.3 kcal mol^{-1} at 25 °C, respectively (Figure 2).[11] From these data, the half-lives of the optical activity ($t_{1/2}$) of **3a** and **3b** at 25 °C were calculated as 2 × 10^{-6} s and 5 × 10^{-5} s, respectively. These results show that i) **3a** and **3b** do not have isolable enantiomers in a practical sense, ii) the planar chirality of **3a** and **3b** is significantly less stable than that of cyclophyne analogue **2a** (X = Ts) ($\Delta G^{\ddagger}$ = 15.1 kcal mol^{-1}, $t_{1/2}$ = 6 × 10^{-3} s at 25 °C), and iii) the substituent R on the alkene moiety has a certain level of influence on the stereochemical stability of **3**.[12]

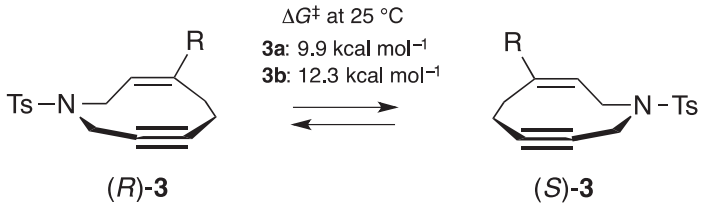


Figure 2. Dynamic chirality of **3**

In summary, we have described an efficient approach to the nine-membered enyne nitrogen heterocycles **3a** and **3b**. The newly synthesized compounds showed fairly labile planar chirality in solution at ambient temperature; their enantiomers are unisolable in a practical sense. Further detailed studies on the relationship between the structures and stereochemical stability of these enyne heterocycles and their synthetic applications are in progress.

ACKNOWLEDGEMENTS

This research was supported by JSPS KAKENHI Grant Number 24350048, and MEXT Project of Integrated Research on Chemical Synthesis.

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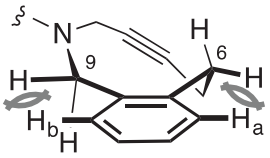
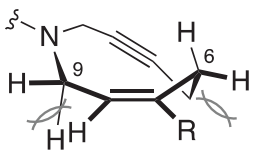
8. **3a**: a colorless crystal; IR (crystal using a diffuse reflector) cm^{-1}: 2939, 2227, 1597, 1157, 1098, 657; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.69 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.82-5.73 (m, 1H), 5.62-5.53 (m, 1H), 3.90 (s, 2H), 3.81 (d, J = 8.1 Hz, 2H), 2.43 (s, 3H), 2.34-2.28 (m, 2H), 2.17-2.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 143.6, 135.8, 131.7, 129.9, 128.0, 127.3, 94.6, 83.4, 44.2, 39.7, 27.0, 21.6, 19.1.
9. **3b**: a colorless crystal; IR (crystal using a diffuse reflector) cm^{-1}: 2923, 2234, 1597, 1447, 1348, 1160, 1092, 657; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.68 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 5.54 (dt, J = 1.2, 8.1 Hz, 1H), 4.20-3.40 (br, 4H), 2.43 (s, 3H), 2.40-2.15 (br, 4H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 143.4, 135.5, 135.2, 129.8, 127.1, 125.9, 95.1, 83.4, 45.4, 39.7, 32.1, 24.5, 21.7, 18.2.
10. Deposition number CCDC-1020694 for compound **3b**. Selected crystallographic data: triclinic, P–1 (No. 2), a = 6.8112(11) Å, b = 8.1570(13) Å, c = 13.487(3) Å, α = 79.760(11), β = 79.401(10), γ = 82.719(11), V = 721.4(2) $Å^3$, Z = 2, R_1 = 0.0682, wR_2 = 0.1998. Free copies of the data can be

obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

11. DFT calculations were performed at B3LYP/6-311G(2d,2p) level of theory with Gaussian 09 package. Frisch, M. J. et al. *Gaussian 09, Revision C.01*; Gaussian, Inc.: Wallingford CT, 2010.
12. The DFT calculations show that the transition state for the racemization of **2** and **3** involves the flipping of the benzene ring or *Z*-alkene moiety, respectively (**TS-2** and **TS-3**). The energy barrier for racemization of **2** is higher than that of **3**, due to the substantial 1,3-steric repulsion between the C6 and C9 methylene protons and the H_a or H_b protons of benzene ring. On the other hand, the flipping of alkene of **3a** (R = H) can proceed without such steric repulsion. Racemization of **3b** (R = Me) needs a slightly higher energy than that of **3a**, to overcome the 1,2-steric repulsion between the C6 proton and the methyl group.



TS-2



TS-3