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An imino Nazarov cyclization

Marcus A. Tius,* Chester C. Chu and Raquel Nieves-Colberg

Department of Chemistry, University of Hawaii, 2545 The Mall, Honolulu, HI 96822, USA

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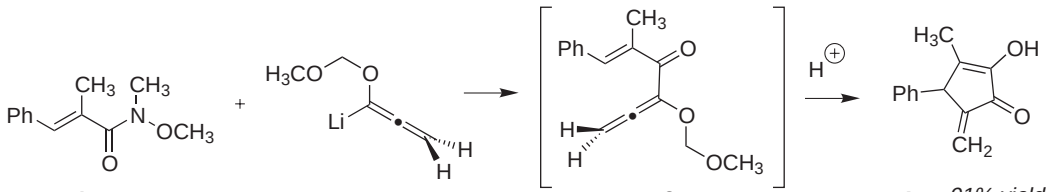
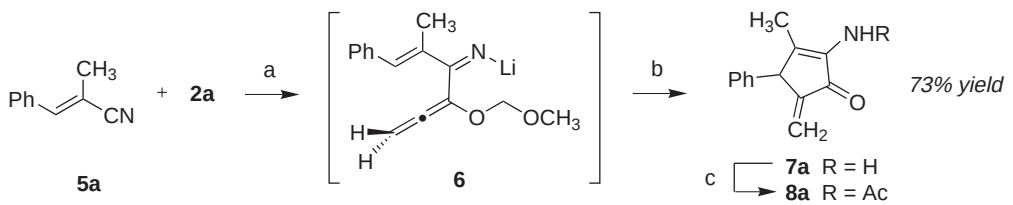
Abstract—α-Aminocyclopentenones are available in a single operation from α,β-unsaturated nitriles and (methoxy)-methoxyallenes. The cyclization is equivalent to an imino Nazarov reaction. © 2001 Elsevier Science Ltd. All rights reserved.

In earlier work we have described several variants of the classical Nazarov reaction[1] in which allenyl ketones[2] or allenyl alcohols[3] were cyclized to cross-conjugated cyclopentenones. For example (Eq. (1)), Weinreb amide **1** underwent addition with allenyl nucleophile **2a** to produce the putative intermediate ketone **3** which underwent spontaneous cyclization to cyclopentenone **4** in high yield upon workup.[4] We wondered whether addition of allenyl nucleophiles to α,β-unsaturated nitriles might lead to imine intermediates, acid-catalyzed cyclization of which would generate α-aminocyclopentenones. Such a reaction would be potentially very useful, inter alia, for alkaloid synthesis.

Our preliminary results are summarized in Scheme 1. Addition of α-lithio-α-(methoxy)methoxyallene[5] **2a** to α-methylcinnamonitrile **5a** at −78°C led to a solution of lithioimine **6**, which was quenched with saturated aqueous ammonium dihydrogen phosphate. Protonation of **6** was followed by spontaneous cyclization to α-aminocyclopentenone **7a**. This material could be isolated following aqueous workup and flash column chromatography on silica gel, however, it was much more convenient to convert crude **7a** to acetamide **8a**, and then perform the chromatographic purification on **8a** (vide infra). A number of protic acids under a variety of reaction conditions were examined for the cyclization





Scheme 1. (a) THF, −78°C, 1 h; (b) satd aq $(NH_4)H_2PO_4$, −78°C to rt, 30 min; (c) Ac_2O, pyr, cat. DMAP, rt, 18 h.

Keywords: amino ketones; allenes; enamines; Nazarov reactions.

* Corresponding author. Tel.: 808-956-2779; fax: 808-956-5908; e-mail: tius@gold.chem.hawaii.edu

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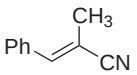
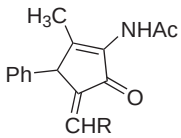
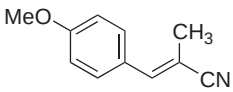
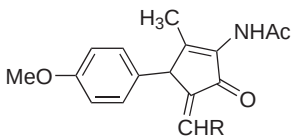
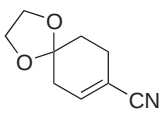
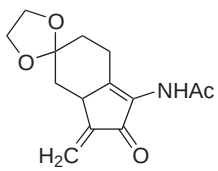
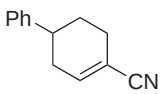
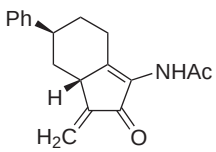
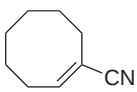
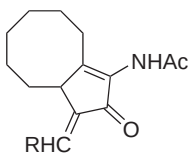
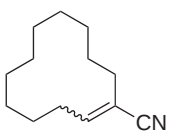
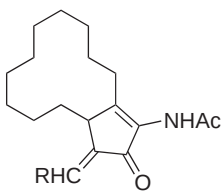
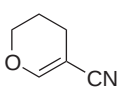
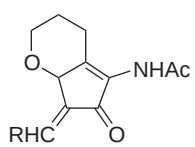
step leading to **7a**. Best results were obtained with ammonium dihydrogen phosphate.

The α,β-unsaturated nitrile starting materials were prepared through straightforward application of conventional methods.[6] The scope of the cyclization can be assessed through the examples listed in Table 1.[7]

Overall yields of the cyclized products were generally good. However, in the case of **5c**, product **8c** was accompanied by significant quantities of diene **9** (40% isolated yield). The appearance of this byproduct is due to competing γ-deprotonation of **5c**, followed by cleavage of one of the two C–O bonds of the ethylene ketal function. Acetylation of the free hydroxyl group led to **9**. The α,β-unsaturated nitriles were less reactive as electrophiles than the α,β-unsaturated Weinreb- and morpholino amides which we had examined previously. The reaction of cinnamonitrile failed to produce cyclic product, so it appears that a non-hydrogen substituent at the α-carbon atom of the unsaturated nitriles is required.[4]

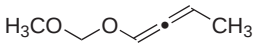
In earlier work we had shown that in cyclopentannelations with γ-substituted allenes, the *Z* isomers at the exocyclic double bond of the cyclic products are kinetically favored.[8,9] Therefore, the variation in the isomeric ratios of products derived from allenes **2b** and **c**,[10] which

Table 1. Aminocyclopentenones[a]

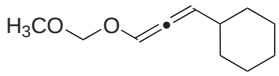
nitrile	allene	product	yield (*E/Z* ratio)
 **5a**	**2a** **2b**		**8a** (R = H) *73%* **9a** (R = Me) *71% (2/1)*
 **5b**	**2a** **2b** **2c**		**8b** (R = H) *63%* **9b** (R = Me) *70% (>95/5)* **10b** (R = C_6H_{11}) *60% (1/1)*
 **5c**	**2a**		**8c** (R = H) *46%*
 **5d**	**2a**		**8d** (R = H) *51%*
 **5e**	**2a** **2b**		**8e** (R = H) *72%* **9e** (R = Me) *68% (1/1)*
 **5f**	**2a** **2b**		**8f** (R = H) *65%* **9f** (R = Me) *52% (1/1)*
 **5g**	**2a** **2b** **2c**		**8g** (R = H) *67%* **9g** (R = Me) *65% (>95/5)* **10g** (R = C_6H_{11}) *92% (4/1)*

[a] Yields refer to isolated overall yields (two steps) of chromatographed products. Isomeric ratios were determined gravimetrically, following chromatography, with the exception of **10g**, in which case the ratio of isomers was estimated by ^{1}H NMR.

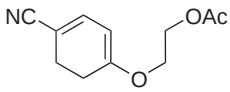
are reported in Table 1 probably reflects different degrees of isomerization of the kinetically formed *Z* isomers to the thermodynamically favored *E* isomers. The isomerization takes place during the acid-catalyzed cyclization, but also during the acetylation step.



2b

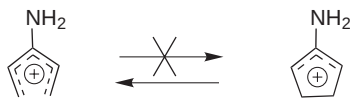


2c



9

The α-aminocyclopentenones (e.g. **7a**) were isolable as pure products following flash column chromatography on silica gel, but they were not stable to storage. Decomposition to produce dark, viscous material took place with an induction period which was not consistent from run to run. The decomposition pathway is probably polymerization by nucleophilic attack of the free amino group of one molecule upon the activated enone of another, and may be catalyzed by adventitious acid. In contrast to the free amines, the acetamides were stable to storage for several weeks at room temperature.



11 **12** (2)

It is noteworthy that calculations by Smith[11] have indicated that the classical imino Nazarov reaction is energetically disfavored: the calculated difference in energy between the acyclic pentadienyl cation **11** and the cyclic allyl cation **12** invariably favors the acyclic product (Eq. (2)). Electron donation by the amino group in **11** stabilizes the ring-open cation. In the present work, an unfavorable equilibrium for the cyclization can be overcome by irreversible loss of methoxymethyl cation in the next step.[12] It is important to emphasize that cleavage of an oxocation from the cyclic intermediate appears to be critical to the success of all the cyclopentannelations involving alkoxyallene intermediates, because it is the step which effectively terminates the reaction and shuts down undesired processes of the cyclic cation which would erode the yield.[13]

In conclusion, an imino Nazarov reaction has been described which gives rise to cross-conjugated α-aminocyclopentenones. These materials can be prepared in a single operation from readily available α,β-unsaturated nitriles, and are potentially useful starting materials for alkaloid synthesis. We are not aware of any other published examples of an imino Nazarov reaction.[14]

Acknowledgements

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6. Nitriles **5a**, **b** and **g** were prepared from the corresponding enals by dehydration of the corresponding oximes: Attanasi, O.; Palma, P.; Serra-Zanetti, F. *Synthesis* **1983**, 741–742. Nitriles **5c–f** were prepared by dehydration of the corresponding cyanohydrins: Carruthers, N. I.; Garshab, S.; McPhail, A. T. *J. Org. Chem.* **1992**, *57*, 961–965; Allen, W. S.; Bernstein, S. *J. Am. Chem. Soc.* **1955**, *77*, 1028–1032.
7. Representative procedure: *N*-(5-methyl-3-methylene-2-oxo-4-phenylcyclopent-1(5)-enyl)acetamide **8a**. To a solution of 365 μL (3.37 mmol) of allene **2a** in 6 mL THF at −78°C was added 1.26 mL of *n*-BuLi in hexanes (2.38 M). After 30 min a solution of 215 mg (1.50 mmol) of α-methylcinnamonitrile **5a** in 4.8 mL THF was added, and the mixture stirred for 1 h. Quenching with 20 mL satd aq $(NH_4)H_2PO_4$, followed by warming to rt and basification with satd Na_2CO_3 gave a crude product which was extracted (3×) with EtOAc, washed with brine and dried over Na_2SO_4. Without evaporation of the solvent, crude 2-amino-3-methyl-5-methylene-4-phenylcyclopent-2-en-1-one **7a** in ca. 30 mL EtOAc was cooled to 0°C and treated with 710 μL (7.50 mmol) of acetic anhydride, 660 μL (8.25 mmol) of pyridine and a small crystal of DMAP. The mixture was stirred overnight, quenched with satd NH_4Cl and extracted (3×) with EtOAc. The organic layer was washed with KH_2PO_4 followed by $NaHCO_3$ and was dried over $MgSO_4$. Flash column chromatography on silica gel afforded 264 mg (73% yield) of **8a** as a pale yellow solid: mp 136–138°C; R_f=0.33 (10% isopropanol in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (br s, 1H), 7.33–7.27 (m, 5H), 6.14 (s, 1H), 5.22 (s, 1H), 4.34 (s, 1H), 2.20 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.2 [C], 168.2 [C], 160.2 [C], 145.2 [C], 139.2 [C], 135.8 [C], 128.7 [CH], 127.8 [CH], 127.3 [CH], 118.5 [CH_2], 52.2 [CH], 23.4 [CH_3], 16.9 [CH_3]; IR (neat) 3290, 1700, 1640 cm^{-1}; mass spectrum (*m*/*z*) 241 (M^+, 83), 199 (93), 184 (87), 69 (100); HRMS: calcd for $C_{15}H_{15}NO_2$, 241.1103; found 241.1108. Data for **7a**: R_f=0.28 (20% EtOAc in hexanes); ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.33–7.25 (m, 5H), 6.07 (s, 1H), 5.10 (s, 1H), 4.19 (s, 1H), 3.65 (br s, 2H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3 [C], 146.2 [C], 143.0 [C], 141.1 [C], 137.6 [C], 128.8 [CH], 128.1 [CH], 127.2 [CH], 117.1 [CH_2], 51.3 [CH], 13.1 [CH_3]; IR (neat) 3480, 3380, 1685, 1635, 1585 cm^{-1}; mass spectrum (m/z) 199 (M^+, 75), 184 (100), 170 (92), 156 (63), 122 (46), 77 (33); HRMS: calcd for $C_{13}H_{13}NO$, 199.0997; found 199.0998.

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10. The allenes were prepared through base-mediated isomerization of the corresponding propargyl methoxymethyl ethers. For an example, see: Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem*. **1998**, *63*, 5971–5976.
11. Smith, D. A.; Ulmer, II, C. W. *J. Org. Chem*. **1997**, *62*, 5110–5115.
12. Relief of the strain associated with the allene function also favors the cyclic product.
13. A long-lived cyclic cation derived from a Nazarov process may be desirable in some instances. Professor West has used such a species to initiate a cation-olefin cyclization: Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc*. **1999**, *121*, 7443–7444.
14. An imino-Prins reaction which leads to α-aminocyclopentenones has been described: Gil, G.; Zahra, J.-P. *Tetrahedron Lett*. **1985**, *26*, 419-420. We thank a referee for alerting us to this publication.