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A facile two-carbon ring expansion process based on the 2-cyano-1-vinylcycloalkanol system

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Abstract

Upon exposure to potassium hydride in THF in the presence of 18-crown-6, several 2-cyano-1-vinylcycloalkanol derivatives were found to undergo ring enlargement to give the corresponding γ-cyano cycloalkanones in synthetically useful yields. © 1999 Elsevier Science Ltd. All rights reserved.

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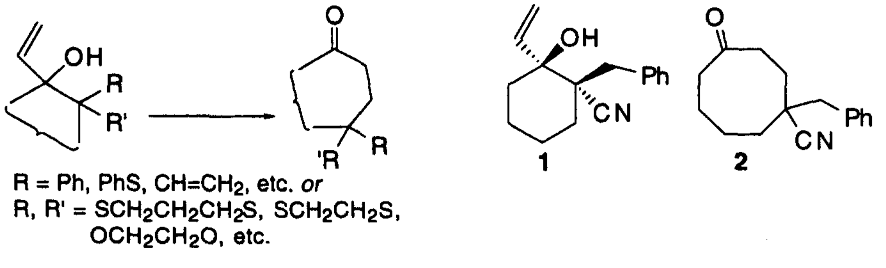
There have been extensive studies in recent years on two-carbon ring expansion via rearrangement of the 1-vinylcycloalkanol system with an activating group attached to C-2 (Scheme 1).[1,2] In spite of a large variation of activating groups studied, the process does not appear to be highly useful in general. With the exception of the strained cyclobutanol system[3] and a few conformationally rigid molecules,[4] the reaction often led to the formation of a complex mixture. We have now observed that the cyano group can serve as an effective activating group. With the assistance of this functionality, a variety of 1-vinylcycloalkanols were shown to undergo two-carbon ring expansion with facility.



Scheme 1.

The ring expansion of 2-cyano-1-vinylcycloalkanols was readily effected by treatment with potassium hydride in THF in the presence of a small amount of 18-crown-6. A typical experiment is as follows. To

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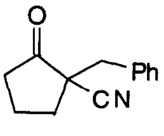
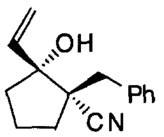
a suspension of potassium hydride (35% in mineral oil, 174 mg, 1.52 mmol, pre-washed with *n*-hexane) in THF (6 mL) at 0°C under a nitrogen atmosphere, were sequentially added THF solutions (5 mL each) of vinyl alcohol **1**[5] (122 mg, 0.51 mmol) and 18-crown-6 (201 mg, 0.76 mmol). The reaction mixture was heated under reflux for 3 h, chilled to 0°C, and acidified with saturated NH_4Cl and 2N HCl (4 mL each). Work-up in the usual manner with ether extraction gave cyano ketone **2** (88 mg, 72% yield) after chromatographic purification (silica gel, 10% ethyl acetate in *n*-hexane). This two-carbon ring expansion process is apparently general. A variety of 2-cyano-1-vinylcycloalkanols (**1**, **3–10**) with diverse ring sizes (five-, six-, seven- and 12-membered rings) were examined. As shown in Table 1, in each case the ring enlargement occurred readily giving rise to the corresponding γ-cyano cycloalkanone (**2**, **11–18**) in synthetically useful yield (51–86%). It is noteworthy that the rearrangement of the five-membered ring compounds (entries 5–7) was extremely facile; each reaction was shown to be complete within 10 min. Even for the formation of mid-sized eight- (entries 1–3 and 8) and nine-membered rings (entry 9), respectively, from six- and seven-membered starting substrates, the reaction also took place rather smoothly within a short period of time (2–6 h) with the exception of the transformation of compound **4**[5] to **12**[7] (entry 3) which took about one day. The process is also applicable to the preparation of large ring ketones. A case in evidence is the rearrangement of 1-vinyl-1-cyclododecanol **5**[8] which gave, after 1 h, the corresponding 14-membered ring ketone **13** (entry 4).

The starting 2-cyano-1-vinylcycloalkanols were readily prepared by treatment of the corresponding 2-cyanocycloalkanones[9] with vinylmagnesium bromide with or without the presence of cerium(III) chloride.[10] As expected, with the assistance of cerium chloride the yields were generally enhanced. This was particularly true with the five-membered ring compounds. In all of these cases, when vinylmagnesium bromide was used, the desired product was obtained in low yield (~40%) along with the recovered starting material even after a long period of reaction time. With the addition of cerium chloride, however, yields were greatly enhanced. As an example, when cyano ketone **19** was treated with vinylmagnesium bromide (THF, –78°C, 3 h), the desired addition products were formed in 43% yield along with a 17% recovery of the starting material. When the reaction was carried out with pre-formed cerium chloride–vinylmagnesium bromide complex under the same conditions, adduct **6a**[5] and its diastereomer **6b** (1:1) were produced in virtually quantitative yield.

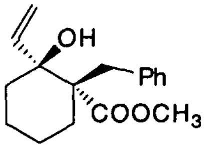
The above results suggest that the cyano group is a useful activating group which makes the two-carbon ring expansion via the 1-vinyl-1-cycloalkanol system a viable general synthetic process. The cyano group appears to be quite unique in this regard. In sharp contrast to compound **1** which gave the ring enlargement product **2** in good yield, the corresponding carbomethoxy derivative **20** underwent extensive decomposition upon exposure to potassium hydride under similar conditions.



19



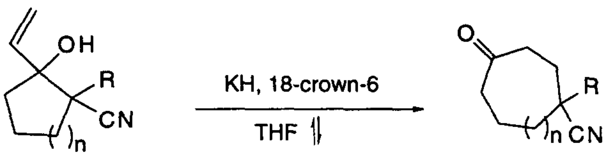
6a

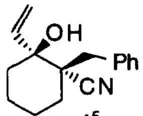
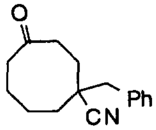
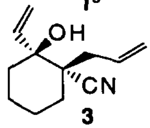
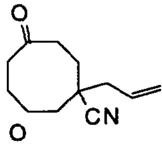
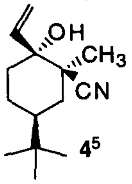
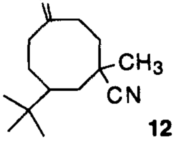
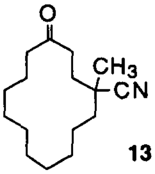
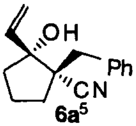
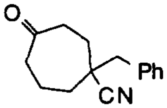
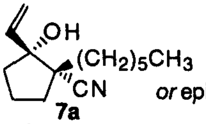
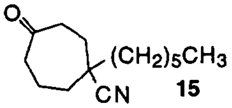
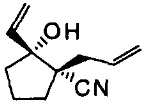
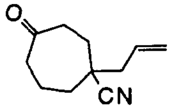
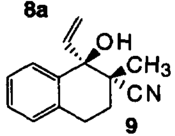
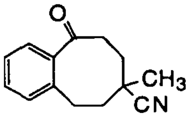
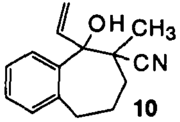
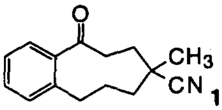


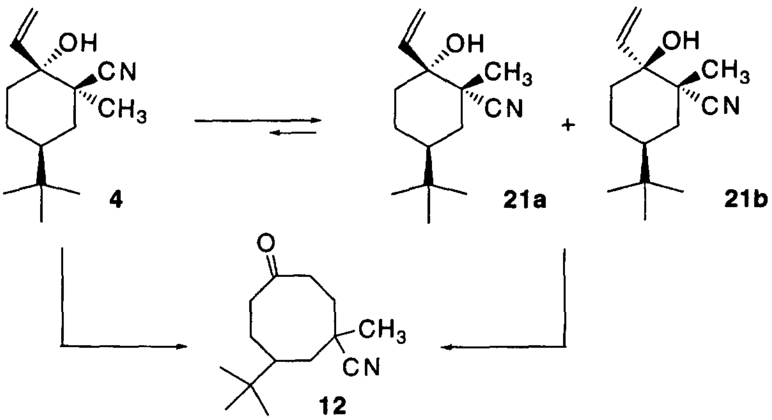
20

Mechanistically, two pathways have been proposed for the two-carbon ring expansion process involving 1-vinyl-1-cycloalkanols, namely, the concerted [1,3] sigmatropic rearrangement and the stepwise ring opening and closure process.[3c,11] In the present case, the latter pathway appears to be in operation as suggested by the following observations. Upon treatment with potassium hydride under the aforementioned conditions for 3 h, cyano alcohol **4** was completely consumed, and its diastereomers **21a** and **21b** (1.5:1) were formed in 58% yield along with a 21% yield of the ring enlargement product **12**[7], which was also produced in 71% yield upon further treatment of **21a** and **21b** (Scheme 2).[6]

Table 1
Two-carbon ring expansion of 2-cyano-1-vinylcycloalkanols



Entry	Substrate[6]	Time	Product[6]	% Yield
1	 1[5]	3 h	 2	72
2	 3	4 h	 11	54
3	 4[5]	22 h	 12	71[7]
4[8]	 5	1 h	 13	51
5	 6a[5] *or* epimer **6b**	10 min	 14	~65
6	 7a *or* epimer **7b**	5 min	 15	~65
7	 8a *or* epimer **8b**	10 min	 16	~55
8	 9	6 h	 17	81
9[8]	 10	2 h	 18	86



Scheme 2.

Acknowledgements

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5. The structure of this compound was confirmed by X-ray analysis.
6. Representative spectral data: compound **1** (mp 97°C (ethyl acetate/*n*-hexane)): IR (cast, $CHCl_3$): 3465 (OH), 2235 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.23 (m, 5H), 6.30 (dd, J_1=17.2 Hz, J_2=10.7 Hz, 1H), 5.47 (d, J=17.2 Hz, 1H), 5.35 (d, J=10.7 Hz, 1H), 2.99 (d, J=13.5 Hz, 1H), 2.77 (d, J=13.5 Hz, 1H), 2.02 (m, 2H), 1.76–1.42 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3 (CH), 135.6 (C), 130.5 (CH), 128.1 (CH), 126.9 (CH), 122.1 (C), 115.2 (CH_2), 74.2 (C), 46.5 (C), 38.3 (CH_2), 36.1 (CH_2), 29.1 (CH_2), 22.2 (CH_2), 20.0 (CH_2); HRMS: calcd. for $C_{16}H_{19}NO$: 241.1467; found: 241.1462; compound **2**: IR (neat, cm^{-1}): 3030 (aromatic C–H), 2231 (CN), 1698 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.23 (m, 5H), 2.83 (d, J=14.2 Hz, 1H), 2.69–2.61 (m, 1H), 2.60–2.41 (m, 3H), 2.59 (d, J=14.2 Hz, 1H), 2.31–2.23 (m, 1H), 2.11–2.02 (m, 1H), 2.10–1.70 (m, 5H), 1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.9 (C), 135.0 (C), 130.2 (CH), 128.5 (CH), 127.5 (CH), 122.9 (C), 43.7 (CH_2), 42.5 (C), 40.3 (CH_2), 39.7 (CH_2), 33.3 (CH_2), 31.2 (CH_2), 28.3 (CH_2), 23.2 (CH_2); HRMS: calcd. for $C_{16}H_{19}NO$: 241.1467; found: 241.1465.
7. An inseparable mixture of two diastereomers (9:1) was obtained.
8. An inseparable mixture of two diastereomers (1:1) was used as the starting material.
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