K_2CO_3/NaI-Induced Cyclization of ω-Bromo α-Cyano Ketones: A New Annulation Approach for the Formation of Carbalkoxycyclohexane Ring System

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Received: 19.03.2012; Accepted after revision: 29.04.2012

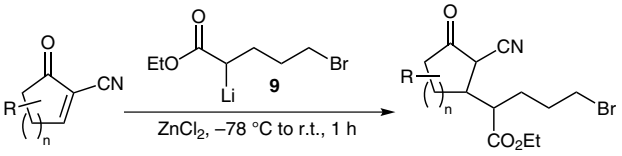
Abstract: An operationally simple and highly effective annulation process, making use of $ZnCl_2$-catalyzed Michael addition and K_2CO_3/NaI-induced cyclization as key manipulations, has been developed to construct various bicyclic systems with a high level of functionalization valuable for further synthetic elaboration.

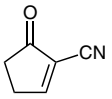
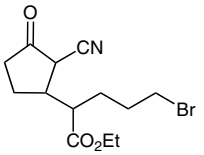
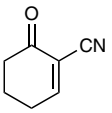
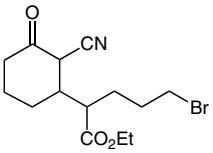
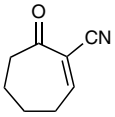
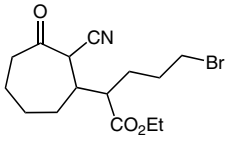
Key words: bicyclic compounds, α-cyano ketones, Michael addition, annulation, cyclization

Methodologies intended for new carbon–carbon bond formation accompanying with a high level of functionalization are considered significant and constantly attract attention from synthetic chemists. During the past three decades, great effort has been dedicated to developing various annulation processes in our laboratories,[1] many of which have been employed as a key operation in the syntheses of decalin-, icetexane-, lignan-, and hydridane-based naturally occurring compounds.[2] Along these lines, we recently found that α-cyano ketones can serve as versatile intermediates to facilitate a new cyclization process, resulting in the formation of a variety of bicyclic products containing a high level of functionality useful for further synthetic elaboration.

2-Cyano-2-cycloalkenones **1**–**8** used for the present study were readily prepared via a two-step sequence, involving Thorpe–Ziegler condensation[3] of the alkanedinitriles followed by phenylselenenylation–oxidative elimination[4] or a four-step sequence, involving formylation,[5] isoxazole formation and its subsequent rearrangement,[6] and phenylselenenylation–oxidative elimination.[4] Compounds **1**–**8** thus formed were found to be rather unstable in that attempted purification by chromatography resulted in substantial loss of material. Therefore, crude products **1**–**8**, without purification, were used as Michael acceptors in subsequent 1,4-conjugate addition under catalysis with $ZnCl_2$[7] to afford desired adducts **10**–**17** in good yields (80–85%, Table 1). In a typical experiment, 2-cyano-2-cyclohexenone (**2**) was treated with 1.5 equivalents of lithium enolate **9**[8] in THF in the presence of $ZnCl_2$ (1.2 equiv) at –78 °C for two hours to afford product **11** as an inseparable diastereomeric mixture in 85% yield. The spectral data (NMR, IR, and HRMS) of **11** was in full agreement with the assigned structure.[9] Other catalysts such as Cu(I)[10] and $SnCl_4$[11] were tested, but the outcome was inferior to $ZnCl_2$. As such, similar reaction conditions were then applied to other substrates with different ring sizes to afford a series of structurally diverse ω-bromo α-cyano ketones **10**–**17**, existing in a mixture of keto and enol forms (Table 1).

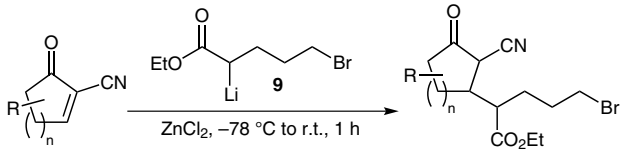
Table 1 1,4-Addition of **9** to 2-Cyano-2-cycloalkenones

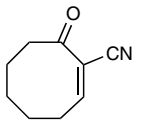
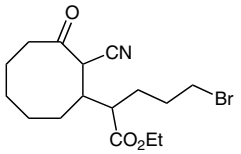
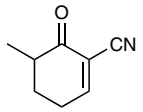
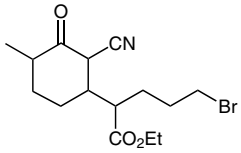
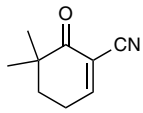
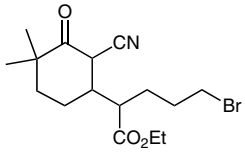
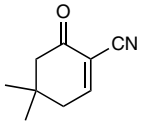
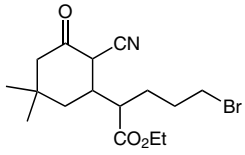
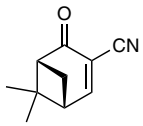
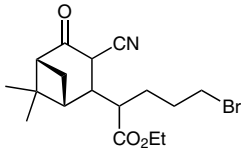


Substrate	Product[a]	Yield (%)[b]
 **1**	 **10**	80
 **2**	 **11**	85
 **3**	 **12**	80

SYNLETT 2012, 23, 1653–1656
Advanced online publication: 14.06.2012
DOI: 10.1055/s-0031-1290386; Art ID: ST-2012-W0253-L

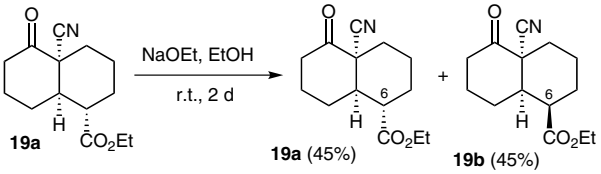
Table 1 1,4-Addition of **9** to 2-Cyano-2-cycloalkenones (continued)



Substrate	Product[a]	Yield (%)[b]
 **4**	 **13**	82
 **5**	 **14**	85
 **6**	 **15**	82
 **7**	 **16**	80
 **8**	 **17**	83

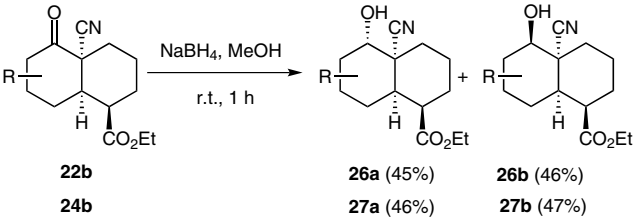
[a] The ratio of isomers could not be unequivocally determined due to facile keto–enol tautomerization.
[b] Yields are for isolated, chromatographically pure products.

With these compounds in hand, the newly designed K_2CO_3/NaI-induced cyclization process was then explored.[12] The expected annulation did occur efficiently to give rise to bicyclic products in excellent yields (90–98%) as illustrated in Table 2. As a typical example, upon treatment with 1.1 equivalents of K_2CO_3 and 0.5 equivalents of NaI in anhydrous acetone for 12 hours, α-cyano ketone **11** underwent intramolecular cyclization smoothly to furnish bicyclic products **19a** and **19b** in 95% yield. The spectral data of **19a**[13] and **19b**[14] were in full agreement with the assigned structures. The relative configuration of **19b** was unambiguously identified by a single-crystal X-ray analysis.[15] Moreover, the stereochemistry of isomer **19a** was further deduced via a chemical correlation using base-induced epimerization.[16] As shown in Scheme 1, **19a** was partially transformed into **19b** via keto–enol tautomerization under basic media at ambient temperature. The studies strongly support that **19a** and **19b** are structurally epimeric each other based on the C-6 center.



Scheme 1 Base-induced epimerization of **19a**

The generality of this newly developed methodology was further demonstrated with various substrates having different ring sizes (Table 2). Accordingly, the annulation appeared to take place in a completely stereocontrolled manner. On the basis of X-ray analyses, it was found that 6/5 and 6/6 fused adducts, as exemplified by **18b**[17] and **25a**,[18] respectively, preferred to form the *cis* ring junction; 6/7 and 6/8 fused adducts, as indicated by **20a**[19] and **21a**,[20] respectively, potentially cyclized to the *trans* ring junction. These generalities are supported by the fact that products **22b** and **24b** were readily reduced with $NaBH_4$ to produce the corresponding epimeric pairs **26a**, **26b**, **27a** and **27b** (Scheme 2); subsequent X-ray analyses of crystalline compounds **26a**[21] and **27a**[22] clearly revealed the *cis* ring junction for these 6/6 fused adducts.



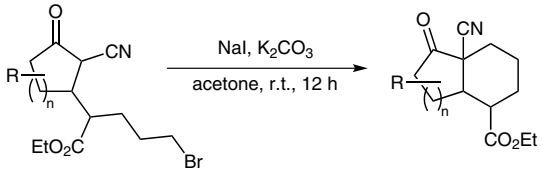
Scheme 2 Production of two hydroxy-epimeric pairs by reduction with $NaBH_4$

Subsequently, the stereochemistry of **18a**, **20b**, **21b**, **22a**, **24a**, and **25b** was fully elucidated via the base-induced epimerization of their counterparts **18b**, **20a**, **21a**, **22b**, **24b**, and **25a**, structures of which have been individually identified by a direct or indirect X-ray crystal structure analysis as described previously.

Tremendous effort has been dedicated to exploring the possibility of changing the above two-step process into a one-pot reaction. After completion of the Michael addition, as monitored by TLC, without purification, NaI (1.2 equiv) or KI (1.2 equiv) was then added in one portion to effect the subsequent cyclization. Although the annulation did occur, the resulting yields are much inferior to those of the aforementioned two-step sequence.

In summary, under induction with K_2CO_3 and NaI, an efficient annulation process for ω-bromo α-cyano ketones has been developed to prepare various bicyclic carbalkoxycyclohexane systems with a high level of functionalization. The newly developed process was expected to be of great utility in light of its operational simplicity, and easy access to readily available 2-cyano-2-cycloalkenone substrates.

Table 2 K_2CO_3/NaI-Induced Annulations of Various ω-Bromo α-Cyano Ketones



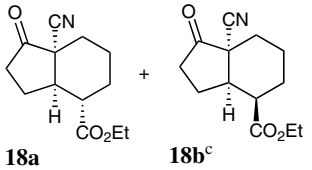
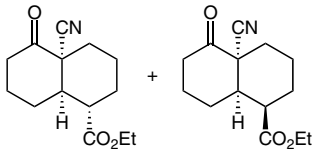
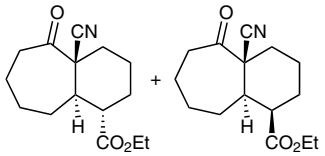
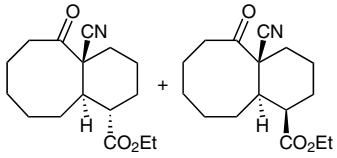
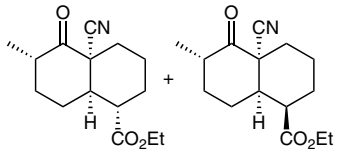
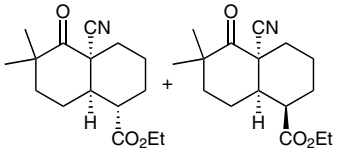
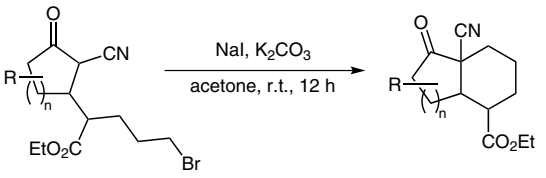
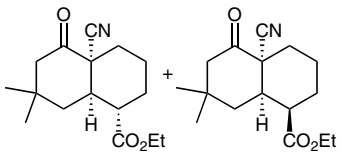
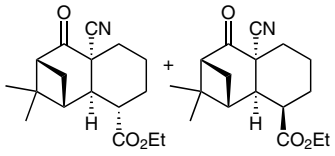
Substrate	Products	Yield (%)[a]	dr
10	 **18a** + **18b**[c]	95[b]	–
11	 **19a** + **19b**[c]	95	1:4
12	 **20a**[c] + **20b**	90	1:1
13	 **21a**[c] + **21b**	98	1:1.7
14	 **22a** + **22b**[c]	95	1:3
15	 **23a**[d] + **23b**[d]	94	1:1

Table 2 K_2CO_3/NaI-Induced Annulations of Various ω-Bromo α-Cyano Ketones (continued)



Substrate	Products	Yield (%)[a]	dr
16	 **24a** + **24b**[c]	97	1:1
17	 **25a**[c] + **25b**	98	1:1

[a] Yields are calculated by a combination of two isolated, chromatographically pure diastereomers.
[b] A mixture of two inseparable diastereomers was produced.
[c] The stereochemistry was assigned based on a single-crystal X-ray analysis.
[d] The *cis* ring junction was tentatively assigned.

Acknowledgment

This work was supported by grants from the National Science Council of Taiwan and China Medical University Hospital (DMR-101-104).

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(7) Demailly, G.; Solladie, G. *J. Org. Chem.* **1981**, *46*, 3102.

(8) **Procedure for the Preparation of Lithium Enolate 9**
To a stirred solution of ethyl 5-bromovalerate (0.58 mL, 3.64 mmol) in THF (4.5 mL) at –78 °C was added LDA (2 M in THF, 2.5 mL, 5.04 mmol) dropwise under nitrogen. The reaction mixture was stirred at the same temperature for 30 min, and the resulting stock solution (7 mL, 0.52 M) was used directly for subsequent 1,4-addition.

(9) **5-Bromo-2-(2-cyano-3-oxocyclohexyl)pentanoic Acid Ethyl Ester (11)**
IR (CH_2Cl_2 cast): ν_{max} = 3431, 2946, 2249, 1731 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 4.23–4.14 (m, 2 H), 3.69 (d, *J* = 12.3 Hz, 0.4 H), 3.52 (d, *J* = 12.0 Hz, 0.6 H), 3.50–3.46 (m, 1 H), 3.43–3.34 (m, 2 H), 2.77–2.73 (m, 0.6 H), 2.67 (dt, *J* = 7.6, 3.3 Hz, 0.4 H), 2.61–2.56 (m, 1 H), 2.47–2.25 (m, 2 H), 2.21–2.01 (m, 2 H), 1.97–1.86 (m, 2 H), 1.85–1.76 (m, 2 H), 1.75–1.58 (m, 1 H), 1.29–1.20 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4 (C), 199.8 (C), 172.9 (C), 172.1 (C), 116.5 (C), 115.5 (C), 61.1 (CH_2), 61.0 (CH_2), 48.2 (CH), 47.7 (CH), 47.4 (CH), 45.1 (CH), 44.2 (CH), 43.3 (CH), 40.4 (CH_2), 40.2 (CH_2), 33.1 (CH_2), 32.0 (CH_2), 30.7 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 25.1 (CH_2), 24.5 (CH_2), 23.6 (CH_2), 14.3 (CH_3), 14.1 (CH_3). HRMS (EI): *m/z* calcd for $C_{14}H_{20}NO_3Br$: 329.0627; found: 329.0625.

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(13) **(1*S**,4a*S**,8a*R**)-4a-Cyano-5-oxodecahydronaphthalene-1-carboxylic Acid Ethyl Ester (19a)**
IR (CH_2Cl_2 cast): ν_{max} = 2950, 2233, 1731, 1715 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 4.10 (q, *J* = 7.1 Hz, 2 H), 2.78 (ddd, *J* = 13.4, 13.0, 7.1 Hz, 1 H), 2.61 (dt, *J* = 8.6, 3.1 Hz, 1 H), 2.48–2.41 (m, 2 H), 2.30–2.19 (m, 2 H), 1.98–1.83 (m, 3 H), 1.73–1.64 (m, 2 H), 1.59–1.46 (m, 3 H), 1.20 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 201.8 (C), 173.3 (C), 120.1 (C), 61.7 (CH_2), 48.9 (C), 44.8 (CH), 42.6 (CH), 38.9 (CH_2), 30.0 (CH_2), 28.4 (CH_2), 25.5 (CH_2), 21.7 (CH_2), 20.3 (CH_2), 14.1 (CH_3). HRMS (EI): *m/z* calcd for $C_{14}H_{19}NO_3$: 249.1365; found: 249.1383.

(14) **(1*R**,4a*S**,8a*R**)-4a-Cyano-5-oxodecahydronaphthalene-1-carboxylic Acid Ethyl Ester (19b)**
IR (CH_2Cl_2 cast): ν_{max} = 2947, 2240, 1737, 1722 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 4.08 (m, 2 H), 2.81 (dt, *J* = 8.5, 4.1 Hz, 1 H), 2.65 (dt, *J* = 8.7, 4.0 Hz, 1 H), 2.49–2.38 (m, 2 H), 2.07–2.03 (m, 1 H), 1.95–1.89 (m, 2 H), 1.85–1.82 (m, 1 H), 1.80–1.75 (m, 1 H), 1.73–1.65 (m, 3 H), 1.64–1.59 (m, 1 H), 1.52–1.48 (m, 1 H), 1.19 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 202.8 (C), 172.6 (C), 118.7 (C), 60.6 (CH_2), 55.1 (C), 42.9 (CH), 42.1 (CH), 36.6 (CH_2), 27.5 (CH_2), 23.9 (CH_2), 21.7 (CH_2), 20.9 (CH_2), 20.5 (CH_2), 14.0 (CH_3). HRMS (EI): *m/z* calcd for $C_{14}H_{19}NO_3$: 249.1365; found: 249.1380. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.49; H, 7.67; N, 5.30.

(15) Crystallographic data have been deposited with Cambridge Crystallographic Data Centre (CCDC 845718).

(16) To a stirred solution of **19a** (10 mg, 0.04 mmol) in EtOH (5 mL) was added NaOEt (8.8 mg, 0.13 mmol) in one portion. The reaction mixture was stirred at r.t. for 2 d and quenched with H_2O (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the crude residue, which was purified by flash chromatography on silica gel with EtOAc–*n*-hexane (1:4) to afford **19a** (4.5 mg) and **19b** (4.5 mg) in a combination of 90% yield.

(17) Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 845716).

(18) Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 845720).

(19) Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 845714).

(20) Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 845715).

(21) Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 845717).

(22) Crystallographic data has been deposited with Cambridge Crystallographic Data Centre (CCDC 845719).

