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New Synthetic Technology for the Mild and Selective One-Carbon Homologation of Hindered Aldehydes in the Presence of Ketones

K. C. Nicolaou,* Georgios Vassilikogiannakis, Remo Kranich, Phil S. Baran, Yong-Li Zhong, and Swaminathan Natarajan

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

kcn@scripps.edu

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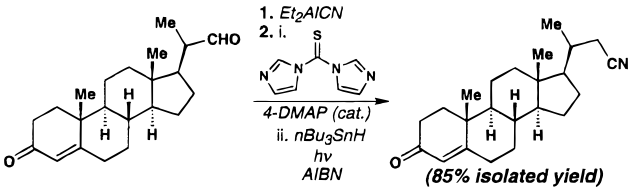
ABSTRACT



A selective, mild, and highly efficient method has been uncovered during the total synthesis of the CP molecules to accomplish the one-carbon homologation of sterically hindered aldehydes in the presence of acid- and base-labile moieties, Michael acceptors, and even other carbonyl groups such as reactive and epimerizable ketones. Mechanistic studies have revealed a neutral reagent for the rapid collapse of cyanohydrins to ketones.

During the course of our recent total synthesis of the CP molecules,[1] the opportunity arose to develop a method for the conversion of aldehyde **1** to the homologated cyanide **2** (Scheme 1). In this model study we focused our attention on homologation at the aldehyde stage since several methods for homologation at either the alcohol or acid stage failed on more complex substrates. Several conventional methods for the homologation of **1** such as the Wittig,[2] Matteson,[3] or other ylide-based[4] protocols led to low yields of the desired product along with byproducts from interference of the ketone moiety. The current strategy was based on the mild formation of cyanohydrins in order to selectively coerce the one-carbon elongation of hindered aldehydes such as **1** even in the presence of exposed ketones. Treatment of **1** with Et_2AlCN[5] (5 equiv) at 0 °C for 5 min led to pure biscyanohydrin **3** after workup. After dissolution in CH_2Cl_2 and selective formation of the mono-thioimidazolide[6] **4**, deoxygenation (nBu_3SnH, AIBN, $h\nu$)[7] ensued within 5 min in the same pot as observed by TLC. To our delight, the deoxygenation sequence delivered not only the coveted one-carbon elongation, but was also attended by concomitant ketone regeneration. The sequence from **1** to **2** required only one

(1) Part 1: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669. Part 2: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1676. For the asymmetric total synthesis of the CP molecules, see: Nicolaou, K. C.; Jung, J.-Q.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829.

(2) Nicolaou, K. C.; Härter, M. W.; Gunzner, J. L.; Nadin A. *Liebigs Ann.* **1997**, 1283.

(3) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535.

(4) Bestmann, H. J.; Zimmerman, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; **1991**; Vol. 6, pp 171−198.

(5) Nagata, W.; Yoshioka, M.; Okumura, T. *Tetrahedron Lett.* **1966**, 847.

(6) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin. Trans. 1* **1975**, 1574.

(7) Critch, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.

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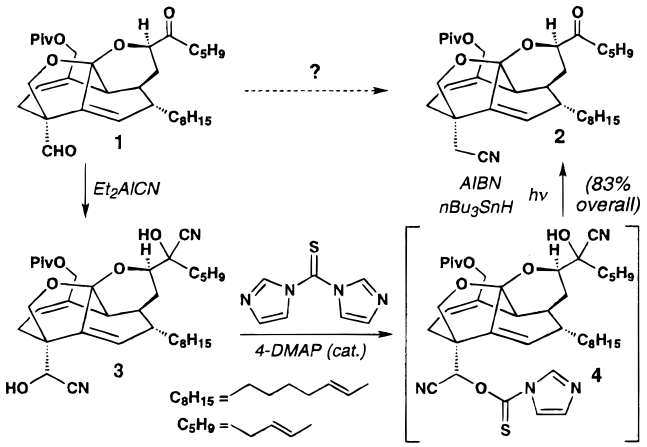
Scheme 1. Mild Conversion of Aldehyde **1** into Cyanide **2** without Protection of the Ketone Present in **1**

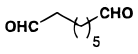
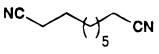
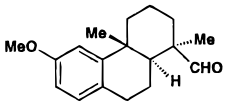
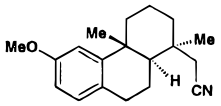
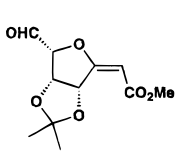
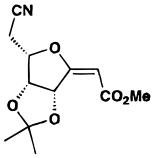
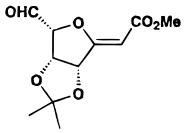
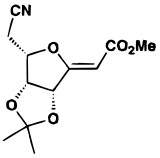
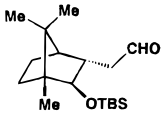
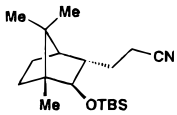
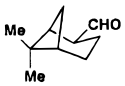
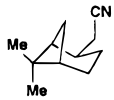
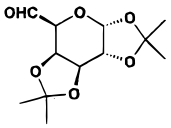
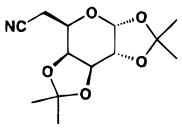


purification and two reaction vessels and proceeded in an overall yield of 83%. Herein we report the generality and scope of this versatile and selective one-pot homologation for hindered aldehydes in the presence and absence of ketones as well as a proposed mechanism for the unusual ketone regeneration observed.

We first set out to investigate the generality of this protocol with simple aldehydes in order to optimize the overall process (Table 1). In all cases, the reactions proceeded as efficiently and easily as for substrate **1** with overall yields ranging from 70 to 99%.

Table 2 illustrates the versatility of this approach with a number of complex and sterically hindered keto-aldehydes. Overall yields are generally good to excellent for the entire procedure (aldehyde → cyanide). The first step is extremely mild since the presence of Michael acceptors (entries 3 and 4, Table 1; entries 1, 2, and 6,[8] Table 2), base-labile (entries 1 and 2, Table 2) and even acid-sensitive (entries 3, 4, 7, Table 1, entries 1−3, Table 2) groups did not influence (bis)-cyanohydrin formation. Even in the case of the extremely hindered aldehyde in entry 7 (Table 2), the reaction succeeds furnishing 80% overall yield of the desired cyanide. Substrates containing easily enolizable carbonyl groups showed no epimerization under the reaction conditions (Table 1, entries 3, 4, and 7; Table 2, entries 1−3, 5, and 6). This strategy saves a number of steps since alternative routes based on protecting group chemistry are lengthy and lower-yielding. Intrigued by the facile and simultaneous deprotection of ketone−cyanohydrins in this neutral reaction, we set out to determine the root of this unusual phenomenon (see Scheme 2). After a systematic elimination of the possible causes for this transformation,[9] we suspected that imidazole, produced after deoxygenation,[7] was responsible. Although the deoxygenation/ketone regeneration of **4** (derived from

Table 1. One-Carbon Homologation of Simple and Hindered Aldehydes

Entry	Aldehyde[a]	Cyanide	Yield[b]
1			82
2			99[c]
3			70
4			71
5			70
6			75
7			85

[a] Preparation of aldehydes in entries 1−7 will be presented in the full account of this work. [b] Isolated yield over entire homologation sequence. [c] Yield based on 11% recovered aldehyde.

(8) 1 equiv of Et_2AlCN was used to avoid Michael addition.

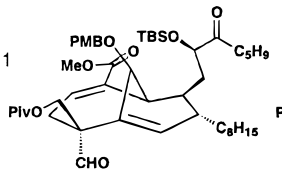
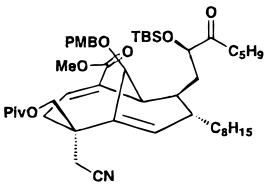
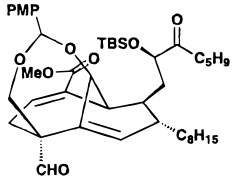
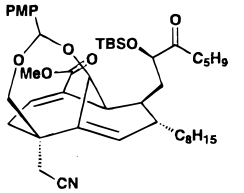
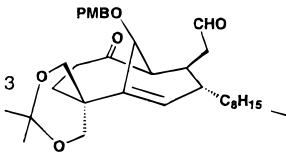
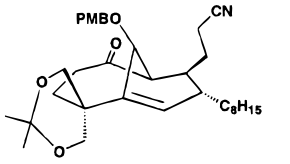
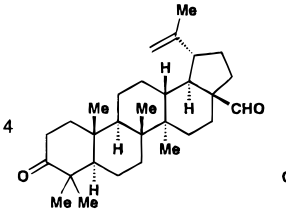
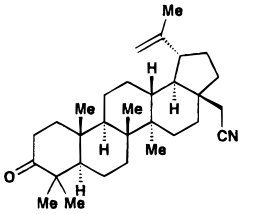
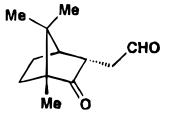
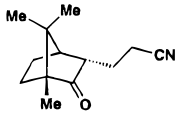
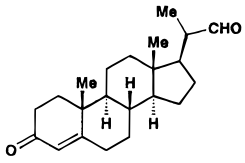
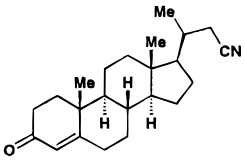
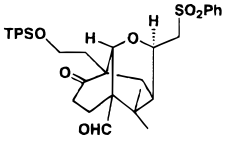
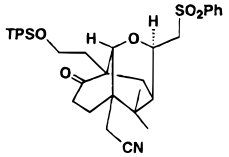
(9) Using the cyanohydrin of cyclohexanone (**8**), the following control experiments were performed: (a) **8** + AIBN; (b) **8** + nBu$_3$SnH; (c) **8** + nBu$_3$SnH + AIBN; (d) **8** + nBu$_3$SnH + AIBN + *hv*; (e) experiment d followed by silica gel chromatography; (f) **8** + 4-DMAP or imidazole. Experiments a−e led to no reaction and full recovery of **8**. Experiment f led to ca. 20% conversion to cyclohexanone after 12 h.

(10) Prepared as reported in Japanese Patent application JP 79-38934 (Sumitomo Chemical Co., Ltd., Japan), see also: *Chem. Abstr. 94*, 139812.

(11) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.

(12) **General Experimental Procedure.** All compounds reported were fully characterized spectroscopically. To a 0.8 M solution of keto-aldehyde (i.e., Table 2) in toluene was added 2.2 equiv of Et_2AlCN (1 M solution in toluene, Aldrich) at 0 °C. After approximately 10 min the reaction mixture was diluted with EtOAc and Rochelle's salt (saturated solution) was added. After stirring for 30 min at ambient temperature, the mixture was separated and the organic layer was washed sequentially with water and brine, dried ($MgSO_4$), and concentrated in vacuo to furnish the bis-cyanohydrin in 90% purity. Only 1−2 equiv of Et_2AlCN is necessary for simple aldehydes (i.e., Table 1). To a degassed (Ar bubbling, 10 min) solution of (bis)cyanohydrin in CH_2Cl_2 (distilled from CaH_2) were added 0.2 equiv of 4-DMAP and 1.1−1.2 equiv of 1,1′-thiocarbonyldiimidazole. Upon formation of the thioimidazolide (as monitored by TLC, usually 5−30 min), nBu$_3$SnH (5.0 equiv), and AIBN (0.2 equiv) were added, and the reaction vessel was placed in a 20 °C water bath while exposed to light from a nearby sunlamp (simple floodlamp) for 5−20 min (TLC monitoring). The reaction mixture was diluted (10:1 hexanes:EtOAc) and passed through a silica plug to remove tin impurities, and the product was eluted with hexanes:EtOAc (1:1). Flash column chromatography was employed to obtain spectroscopically pure material.

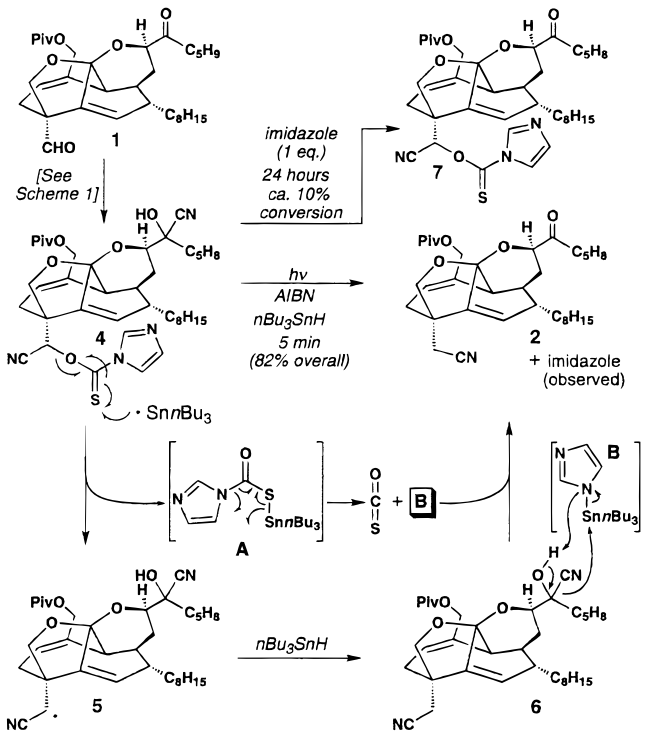
Table 2. Mild and Completely Selective Homologation of Hindered Aldehydes in the Presence of Ketones

Entry	Aldehyde[a]	Cyanide	Yield[b]
1			73
2			78
3			66
4			78
5			82
6			85
7			80

[a] Preparation of aldehydes in entries 1−3 and 5 will be presented in the full account of this work. Aldehydes in entries 4 and 6 were commercially available and aldehyde in entry 7 was generously supplied by J. Pfefferkorn (this group). [b] Isolated yield over the entire homologation sequence.

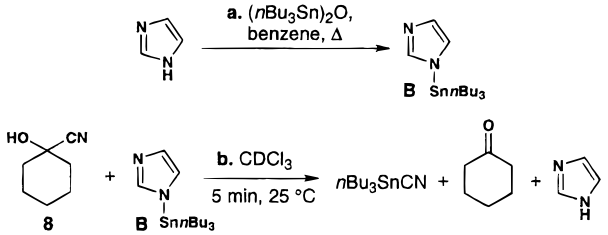
1, Scheme 1) giving rise to **2** occurred in ca. 5 min, treatment of **4** with imidazole (1 equiv) for 24 h led to a very slow conversion (ca. 10%) to ketone **7**. These results suggested that a reactive intermediate produced during the course of the deoxygenation reaction may be responsible for this unique ketone regeneration. Thus, based upon the known mechanism of this deoxygenation,[6,7] we propose that inter-

Scheme 2. Mechanistic Rationale for the Concomitant Regeneration of Ketones from Cyanohydrins during the Deoxygenation of Thioimidazolides



mediate **B** (Scheme 2), derived from intermediate **A**, reacts with **6** as depicted in Scheme 2, leading to the desired product **2**. To verify the presence and participation of intermediate **B** in this reaction, we synthesized it[10] and probed its reactivity with **8** as shown in Scheme 3. Thus, in the presence of **B**, **8**

Scheme 3. Evidence for the Participation of Intermediate **B** in the Regeneration of Ketones from Cyanohydrins



was converted to cyclohexanone quantitatively within 5 min at room temperature as observed by ^{1}H and ^{13}C NMR spectroscopy.

In conclusion, we have developed a new and efficient protocol for the one-carbon elongation of hindered aldehydes even in the presence of ketones, esters, Michael acceptors, and acid- and base-labile groupings. In the case of keto-aldehydes, both the ketone and aldehyde are transformed to cyanohydrins, yet the ketone grouping is regenerated automatically during the reaction via a novel mechanism. Further

discoveries[11] arising from our travels through the CP molecule "synthetic labyrinth" will be reported in due course.[12]

Acknowledgment. We thank Drs. D. H. Huang and G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. This work was financially supported by the National Institutes of Health (USA), The Skaggs Institute for Chemical Biology, a postdoctoral fellowship from Bayer AG (R.K.), a doctoral fellowship from the National Science Foundation (P.S.B.), and grants from Pfizer, Glaxo, Merck, Schering Plough, Boehringer-Ingelheim, Bristol-Myers Squibb, Hoffmann-LaRoche, DuPont, and Abbott Laboratories.

Supporting Information Available: Spectral data (R_f, IR, ^{1}H NMR, ^{13}C, HRMS) for compounds (Table 1, entries 2−7 and Table 2, entries 4−7). Spectral data for CP compounds (Table 2, entries 1−3) will be reported in a full paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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