Autoxidative Annulation Cascade of the α-Cyano β-TMS-capped Alkynyl Cycloalkanone System

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ABSTRACT
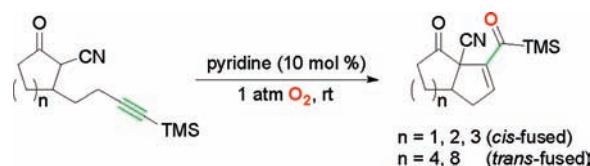
The autoxidative annulation cascade promoted by an α-cyano β-TMS-capped alkynyl cycloalkanone system under catalysis with pyridine in one oxygen atmosphere has proven to be highly viable. On the basis of this newly developed protocol, a variety of highly functionalized bicyclic frameworks can be effectively constructed.

In continuation of our studies on α-activated cross-conjugated cycloalkenone systems in organic synthesis,[1-3] 2-cyano-2-cyclohexenone (**1**)[4] was found to be a highly reactive Michael acceptor to facilitate 1,4-conjugate addition with 1-(trimethylsilyl)-1-butyn-4-yl magnesium chloride to give the corresponding ω-silylacetylenic α-cyano ketone **2** in good yield (Scheme 1).[5,6]

Scheme 1
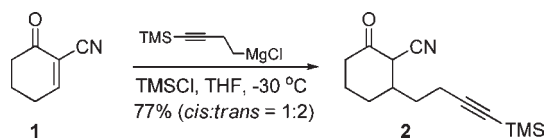
However, we serendipitously discovered that when compound **2** was exposed to air and light on a bench for ca. 3 days, a significant part of it, as detected by TLC analysis in Figure 1, decomposed to a mixture containing two major components. After chromatographic purification and structural analysis, they are assigned as compounds **3** (major) and **4** (minor), respectively, the structures of which were fully characterized by spectroscopic methods (^{1}H and ^{13}C NMR, HRMS, IR, and ^{1}H–^{1}H COSY),[7] and further elucidated by the chemical correlation via converting acylsilane **3** into the corresponding aldehyde **4** under treatment with KF in a cosolvent of THF/H$_2$O.[8] The abnormally large geminal coupling constants detected as 24.8 and 18.8 Hz for **3** and **4**, respectively, are ascribed to the allylic methylene protons,[9] suggesting that they are next to a double or triple bond, and one of them must be parallel to the π orbitals; this spectroscopic characteristic also lends strong support to the previous structural assignment. Encouraged by these preliminary results, closer examination on the

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(1) For a review, see: Wu, Y. K.; Ly, T. W.; Shia, K. S. *Curr. Org. Synth.* **2010**, 7, 78–93.
(2) Chou, H. H.; Wu, H. M.; Wu, J. D.; Ly, T. W.; Jan, N. W.; Shia, K. S.; Liu, H. J. *Org. Lett.* **2008**, 10, 121–123.
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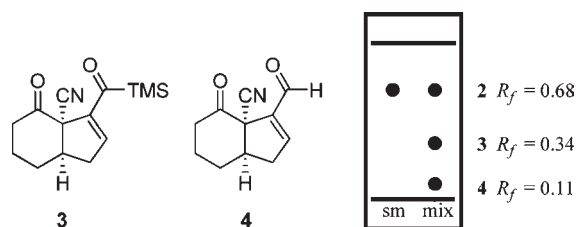(5) Kung, L. R.; Tu, C. H.; Shia, K. S.; Liu, H. J. *Chem. Commun.* **2003**, 2490–2491.

Figure 1. After being exposed to air and light for ca. 3 days, compound **2** was analyzed by TLC (EtOAc/*n*-hexane = 1/2), indicating that a significant part of it has decomposed to compounds **3** and **4**; as determined by ^{1}H NMR, the resulting mixture of **2**, **3** and **4** was in a ratio of 13:6:1.

above reaction was carried out, leading to findings that shortly after flash chromatography and concentration, compound **2**[10] thus obtained must be degassed and stored under N_2 atmosphere at low temperature (< 4 °C); otherwise, as determined by its ^{1}H NMR analysis, upon exposure to air product **3** would be rapidly formed and grew at the expense of starting material **2** as time went by. However, it was noted that the conversion rate proceeded constantly to ca. 30% even after reaction time was prolonged under air for more than two days. Therefore, attempts were then made to optimize reaction conditions, wherein reaction parameters, including solvents, bases, and time, were systematically varied and monitored. As compiled in Table 1, the system (pyridine (catalyst)/O_2 (1 atm)/rt) indicated in entry 11 is tentatively considered to be the method of choice to effect the aforementioned autoxidative reaction.

Accordingly, protic solvents, such as methanol, ethanol, and isopropyl alcohol, appear superior to other aprotic solvents for the reaction. An appropriate weak base was also essential to drive the reaction forward to a

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(7) Satisfactory spectral data were obtained for all new compounds as demonstrated in the Supporting Information. Compound **3**: IR (neat) ν_{max} 2239 (CN), 1721 (C=O, ketone), 1580 (C=O, acylsilane), 1430 (C=C) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.05 (t, *J* = 3.6 Hz, 1H), 3.12−3.03 (m, 1 H), 2.95 (ddd, *J* = 24.8, 9.2, 3.6 Hz, 1H), 2.63−2.55 (m, 1H), 2.44 (ddd, *J* = 24.8, 6.4, 3.6 Hz, 1H), 2.22−2.12 (m, 1H), 2.05−1.77 (m, 3H), 1.57−1.20 (m, 1H), 0.26 (s, 9H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 230.2 (C), 201.0 (C), 148.4 (CH), 146.3 (C), 117.8 (CN), 58.3 (C), 49.9 (CH), 38.7 (CH$_2$), 38.0 (CH$_2$), 26.9 (CH$_2$), 24.2 (CH$_2$), −2.0 (3 × CH$_3$); HRMS (EI) C$_{14}$H$_{19}$NO$_2$Si 261.1185, found 261.1182. Compound **4**: IR (neat) ν_{max} 2240 (CN), 1726 (C=O, ketone), 1681 (C=O, aldehyde), 1428 (C=C) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 9.75 (s, 1H), 7.16 (t, *J* = 2.8 Hz, 1 H), 3.28−3.21 (m, 1H), 2.88 (ddd, *J* = 18.8, 7.2, 2.8 Hz, 1H), 2.72 (ddd, *J* = 14.4, 8.8, 5.6 Hz, 1H), 2.42 (ddd, *J* = 18.8, 6.8, 2.8 Hz, 1H), 2.36−2.29 (m, 1H), 2.16−1.86 (m, 3H), 1.66−1.59 (m, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 201.1 (C), 186.4 (C), 154.6 (CH), 142.7 (C), 117.4 (CN), 56.6 (C), 51.0 (CH), 338.2 (CH$_2$), 37.8 (CH$_2$), 26.5 (CH$_2$), 24.0 (CH$_2$); HRMS (EI) C$_{11}$H$_{11}$NO$_2$ 189.0790, found 189.0782.

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(9) Silverstein, R. M.; Webster, F. X.; Kiemle, D. J. *Spectrometric Identification of Organic Compounds*, 7th ed.; John Wiley & Sons: Hoboken, NJ, 2005; pp 171−172.

(10) Alternatively, substrates **2** and **11**, respectively, can be stored in the eluting solution (ethyl acetate/*n*-hexane = 1:4) at low temperature (< 4 °C) after flash chromatography and used immediately while they are concentrated under reduced pressure.

Table 1. Optimization of Reaction Conditions for the Autoxidative Annulation Process

$$\mathbf{2} \xrightarrow{\text{condition}^a} \mathbf{3}$$

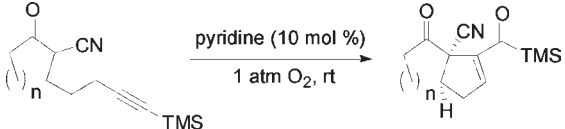| entry	base	solvent	time (h)	yield^b (%)
1	Et$_3$N	CH$_2$Cl$_2$	6	26
2	Et$_3$N	EA	6	10
3	Et$_3$N	THF	6	18
4	Et$_3$N	DMF	6	trace
5	Et$_3$N	MeOH	6	50
6	Et$_3$N	EtOH	6	30
7	Et$_3$N	*i*-PrOH	6	53
8	pyridine	*i*-PrOH	6	60
9	DBU	MeOH	6	trace
10	Et$_3$N	-	12	60
11	pyridine	-	12	70
12	-	-	12	44

^{a} All reactions were performed using substrate **2** (0.4 mmol) and base (0.04 mmol) without or with solvent (1 mL) and vigorously stirred under one oxygen atmosphere at room temperature. ^{b} Yields are for isolated, chromatographically pure products.
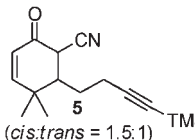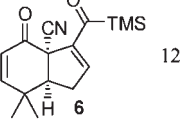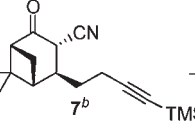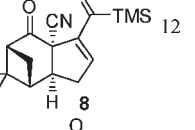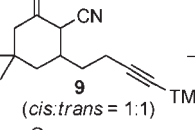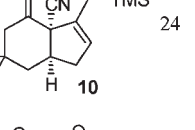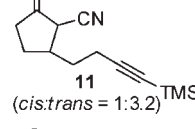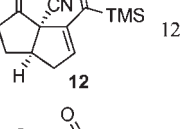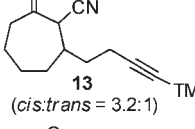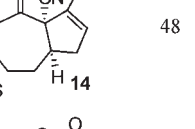
reasonable degree as indicated by entry 11 (70%) vs entry 12 (44%). It is also suggested that a minimum amount of isopropyl alcohol be employed to dissolve the solid reactant as the reaction gets started or to dilute the precipitate, if necessarily, as the reaction proceeds. To verify the generality of this methodology, an investigation of other substrates of greater structural diversity was then undertaken, and results are listed in Table 2.

Unlike substrates 2 and 11[10] incurring ca. 30% transformation into the cyclic products under air after chromatographical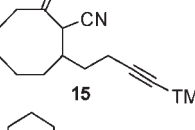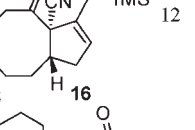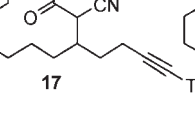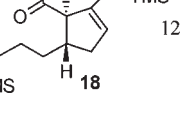 purification and concentration, other substrates examined were relatively more stable and could be handled regularly. The preferential formation of a cyclopentene ring containing an unusual acylsilane moiety was observed for all substrates irrespective of the parent ring size. In addition, a single *cis* stereoisomer was generated in all cases for 5/5, 5/6, and 5/7 fused products, with the exception that the medium- and large-membered ring substrates resulted in *trans*-fused products 16 (5/8) and 18 (5/12), respectively, indicating that for those substrates with more conformational flexibility, the *trans* isomer rather than a *cis* one could be obtained, presumably due to the lower activation energy for the former transition state. The presence of base (e.g., pyridine) is proposed to serve as catalyst to accelerate epimerization of the α-activated carbon center, rendering the substrates assume the most favored conformation with proper orbital alignment to facilitate the annulation cascade. The structure and stereochemistry of all autoxidative coupling products in Table 2 was unambiguously identified by the X-ray crystallographic analysis.[12−18] As well, it is noteworthy that the acylsilane unit thus formed is

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Table 2. Autoxidative Annulation of Various α-Cyano β-TMS-Capped Alkynylcycloalkanones

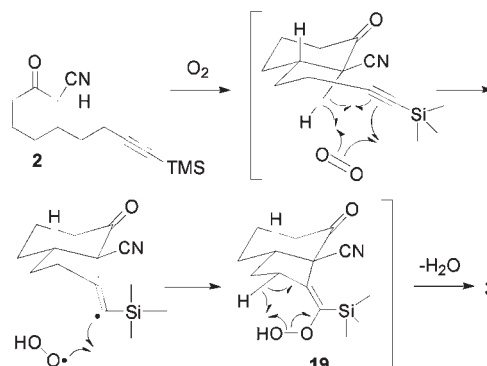| entry	substrate	product	t (h)	yield (%)[a]
1	**5** (cis:trans = 1.5:1)	**6**	12	65
2	**7**[b]	**8**	12	62
3	**9** (cis:trans = 1:1)	**10**	24	52
4	**11** (cis:trans = 1:3.2)	**12**	12	59
5	**13** (cis:trans = 3.2:1)	**14**	48	28[c]
6	**15**	**16**	12	74
7	**17**	**18**	12	62

[a] Yields are for isolated, chromatographically pure products. [b] The stereochemistry was assigned on the basis of NOE experiments.[11] [c] Substrate **13** was recovered intact in 49% yield.

Scheme 2. Proposed Mechanism for the Autoxidative Cyclization Process via the Radical Pathway Initiated by the Ground State Oxygen

The mechanistic rationale for the above autoxidative cyclization is depicted in Scheme 2 using substrate **2** as a typical example. The process is proposed to proceed in a free radical manner with involvement of initial abstraction of the active α-hydrogen by a triplet oxygen followed by intramolecular radical cyclization to give a vinyl radical, which in turn was captured by the hydroperoxide radical to give vinyl peroxide **19** and finally, this unstable species underwent elimination rapidly to furnish the corresponding α,β-unsaturated acylsilane **3**. Moreover, the formation of α,β-unsaturated aldehyde **4** is highly expected to be derived from **3** via Norrish Type I cleavage due to its long-term exposure to light.[19] To clarify the role of the TMS group, substrate **2** was further subjected to deprotection under standard conditions to afford acetylene **20**. Compound **20** thus formed, however, was found to be quite stable after chromatographic purification, and quite stable, and can be handled readily without the necessity for inert gas atmosphere or moisture exclusion.

(12) Crystallographic data for CCDC 797512 (**6**): C$_{16}$H$_{21}$NO$_2$Si, M_w = 287.43, monoclinic, a = 18.561(2) Å, b = 6.4636(8) Å, c = 13.5041(13) Å, V = 1613.9(3) Å^3, space group $P2(1)/n$, Z = 4, a total of 6142 reflections were collected in the range 3.03 < 2θ < 25.03. Of these, 2829 were independent; for the observed data, wR2 = 0.1236, R = 0.0482.

(13) Crystallographic data for CCDC 798461 (**8**): C$_{17}$H$_{23}$NO$_2$Si, M_w = 301.45, orthorhombic, a = 7.1973(2) Å, b = 12.0849(3) Å, c = 19.3543(6) Å, V = 1683.41(8) Å^3, space group $P2(1)/n$, Z = 4, a total of 13835 reflections were collected in the range 1.99 < 2θ < 26.40. Of these, 3438 were independent; for the observed data, wR2 = 0.0984, R = 0.0384.

(14) Crystallographic data for CCDC 798946 (**10**): C$_{16}$H$_{23}$NO$_2$Si, M_w = 289.44, orthorhombic, a = 11.4583(3) Å, b = 12.8713(4) Å, c = 23.1627(9) Å, V = 3416.11(19) Å^3, space group $Pcab$, Z = 8, a total of 13810 reflections were collected in the range 2.37 < 2θ < 24.96. Of these, 2982 were independent; for the observed data, wR2 = 0.1581, R = 0.0710.

(15) Crystallographic data for CCDC 796686 (**12**): C$_{13}$H$_{17}$NO$_2$Si, M_w = 247.37, monoclinic, a = 12.8565(4) Å, b = 6.8971(2) Å, c = 15.8828(6) Å, V = 1334.29(8) Å^3, space group $P2(1)/n$, Z = 4, a total of 10422 reflections were collected in the range 1.78 < 2θ < 26.37. Of these, 2724 were independent; for the observed data, wR2 = 0.1559, R = 0.0573.

(16) Crystallographic data for CCDC 796559 (**14**): C$_{15}$H$_{21}$NO$_2$Si, M_w = 275.42, triclinic, a = 6.8617(12), b = 9.5521(16), c = 11.3029(19) Å, V = 736.4(2) Å^3, space group P-1, Z = 2, a total of 10120 reflections were collected in the range 1.81 < 2θ < 26.45. Of these, 2966 were independent; for the observed data, wR2 = 0.1390, R = 0.0457.

(17) Crystallographic data for CCDC 797513 (**16**): C$_{16}$H$_{23}$NO$_2$Si, M_w = 289.44, monoclinic, a = 12.557(2) Å, b = 12.0022(19) Å, c = 21.455(3) Å, V = 3230.4(9) Å^3, space group $P2(1)/n$, Z = 8, a total of 20907 reflections were collected in the range 1.62 < 2θ < 25.03. Of these, 5700 were independent; for the observed data, wR2 = 0.1152, R = 0.0421.

(18) Crystallographic data for CCDC 799211 (**18**): C$_{20}$H$_{31}$NO$_2$Si, M_w = 345.55, monoclinic, a = 6.6473(11) Å, b = 23.997(4) Å, c = 12.8739(19) Å, V = 2050.2(6) Å^3, space group $P2(1)/n$, Z = 4, a total of 12615 reflections were collected in the range 1.80 < 2θ < 25.03. Of these, 3562 were independent; for the observed data, wR2 = 0.1031, R = 0.0463.

(19) Denmark, S. E.; Xie, M. *J. Org. Chem.* **2007**, *72*, 7050–7053.

was recovered intact under treatment with the preceding optimized reaction conditions over 24 h. Taken together, we can conclude that the TMS moiety is essential for the cyclization, presumably due to its ability to stabilize the proposed sp^2-hybridized vinyl radical by means of the d-orbitals of silicon or through an overlap of the low-lying σ^* (Si−C) orbitals.[20] This radical mechanistic proposal is also supported by the fact that as the reaction was carried out with an extra addition of a radical inhibitor (0.5 equiv. of BTH or DNB),[21] the aforementioned autoxidative cyclization was completely suppressed. However, exactly what controls the autoxidative process of the title system is still not fully understood, and more studies are required to have a better understanding of the mechanism of this exotic reaction.

For comparison purposes, ester **21** was also prepared according to the literature.[22,23] Unexpectedly, this compound was found to be considerably stable under air, and completely inert to autoxidative cyclization under the same reaction conditions applied previously for its α-cyano counterpart **2**. This outcome strongly implies that though both **2** and **21** possess a similar active methine proton prone to enolization, the cyano group might have a unique stereoelectronic factor different from the ester group, thus accounting for the observed aerobic oxidative coupling reaction. Moreover, attempts to prepare α-aldehyde counterpart **22** were also made; unfortunately, all synthetic efforts turned out to be fruitless.
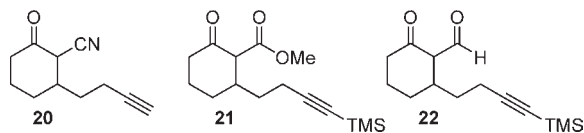
In summary, the autoxidative reaction promoted by α-cyano β-TMS-capped alkynyl cycloalkanones under an oxygen atmosphere with an appropriate base has proven to be highly feasible. On the basis of this newly developed protocol, a variety of bicyclic frameworks containing a high level of functionalization can be effectively constructed. Mechanistically, in addition to the α-cyano moiety playing a role more than just an activating group, the presence of the TMS moiety appears critical for the cyclization, wherein a free radical process, invoking the intermediacy of the σ^* (Si−C) or d-orbitals of the adjacent silicon, is proposed. Indeed, this unusual resonance-stabilizing effect is believed to serve, in part, as the driving force to induce the aerobic annulation cascade in the title system. A full account of this work, including its extension to the synthesis of structurally related natural products,[24−27] will be reported in due course.

Supporting Information Available. Detail experimental procedures and characterization data for all new compounds described in this paper. This material is available free of charge via the Internet at http://pubs.acs.org

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