ORGANIC LETTERS

2012
Vol. 14, No. 23
6024–6027

Tandem Cyclization of α-Cyano α-Alkynyl Aryl Ketones Induced by *tert*-Butyl Hydroperoxide and Tetrabutylammonium Iodide

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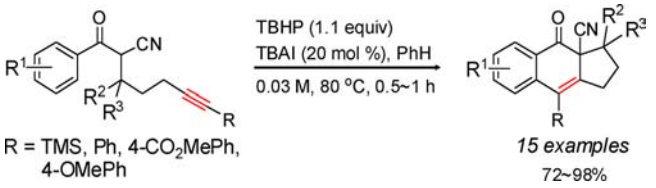
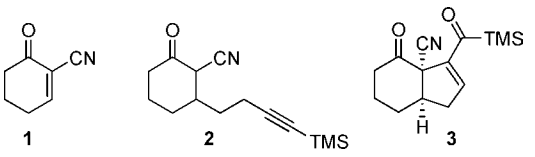
Received October 23, 2012

ABSTRACT



The radical cascade protocol of the α-cyano α-TMS/aryl-capped alkynyl aryl ketones promoted by *tert*-butyl hydroperoxide under catalysis with tetrabutylammonium iodide in refluxing benzene has been developed, leading to the construction of a variety of highly functionalized [6,6,5] tricyclic frameworks in an efficient manner.

During the past decade, a variety of annulation processes based on α-activated cross-conjugated cycloalkenone systems have been developed in our laboratories.[1] As indicated below, α-cyano ketone **2** thus obtained from **1** via 1,4-addition was found to undergo autoxidative cyclization under air to afford product **3** in a significant amount.[2,3]



In continuation of our studies on this unexpected aerobic oxidation, as depicted in Scheme 1, an acyclic benzoylacetonitrile **4** was then synthesized and subjected to the standard reaction conditions previously optimized for α-cyano cycloalkanone substrates.[2] To our surprise, instead of forming the expected acysilane product, compounds **5** and **6** were provided, respectively, in 18% and 30% yields, structures of which were fully characterized by spectroscopic methods, and tricyclic compound **5** was further unambiguously confirmed by the X-ray crystallographic analysis.[4] Mechanistically, the former might be potentially formed via a tandem radical cyclization process and the latter via a direct oxidative cleavage pathway.

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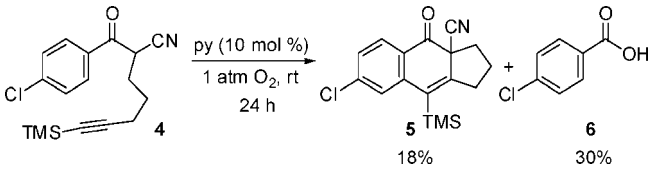
(4) Crystallographic data for CCDC-892910 (**5**): $C_{17}H_{18}ClNOSi$, MW = 315.86, monoclinic, a = 17.1290(12) Å, b = 10.1809(6) Å, c = 19.7805(10) Å, V = 3344.8(3) Å^3, space group $P21/c$, Z = 8, a total of 18471 reflections were collected in the range $2.12 < 2\theta < 25.04$o. Of these, 5875 were independent; for the observed data, wR2 = 0.2132, R = 0.0763.

10.1021/ol3028972
Published on Web 11/28/2012

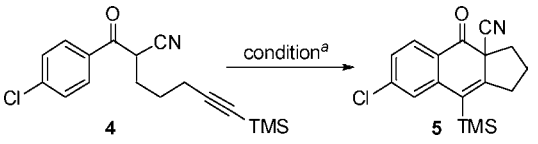
Scheme 1



Facilitating efficient construction of polycyclic rings through [$m + n$] annulations, involving vinyl, imidoyl and/or iminyl radical, remains an important topic in organic synthesis.[5] An intramolecular radical cascade following [4 + 1] and [4 + 2] annulations found in the current case is quite unique and worth further development.[6]

It is conceivable that as oxygen is replaced with other free-radical initiators to promote the reaction, side product **6** should be substantially suppressed and reaction might be exclusively directed toward the desired product **5**. To this end, screening reaction conditions through combination with various radical initiators, solvent systems and reaction concentrations was then extensively carried out, and results are compiled in Table 1.

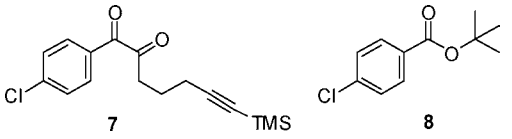
Table 1. Screening of Reaction Conditions



entry	initiator	solvent	conc (M)	temp (°C)	time (h)	yield[b] (%)
1	O_2	DMF	0.2	rt	72	5
2	O_2	toluene	0.2	rt	72	<5
3	O_2 or air	DCM	0.2	rt	72	9
4	Et_3B[c]/air	DMF	0.2	rt	24	45
5	Et_3B[c]/H_2O_2[c]	DMF	0.2	rt	24	30
6	AIBN[d]	toluene	0.1	100	96	32
7	TBHP[d]	PhH	0.1	80	8	10
8	TBHP[d]/TBAI[e]	PhH	0.1	80	1	86
9	**TBHP[f]/TBAI[e]**	**PhH**	**0.03**	**80**	**1**	**95**

[a] All reactions were performed using reactant **4** (100 mg, 0.32 mmol) and a free radical initiator in an amount as indicated below in the selected solvent. [b] Isolated yield. [c] 3.0 equiv was used under N_2. [d] 1.5 equiv was used under N_2. [e] 20 mol % was used. [f] 1.1 equiv was used under N_2.

Low yields of tricyclic product **5** (entries 1−3) in different solvents again confirmed that molecular oxygen was a poor reagent to trigger the observed tandem radical process. Triethylborane (Et_3B) was then attempted.[7] It was found that when Et_3B was incrementally increased up to 3 equiv, the best yield of **5** was obtained in 45% (entry 4) and 30% (entry 5), respectively. Unfortunately, an introduction of oxygen or hydrogen peroxide was necessary for Et_3B to initiate the ethyl radical formation. Consequently, besides **6**, an additional side product **7** (ca. 20%) was detected. Mechanistically, both are assumed to be derived from a common α-carbonyl peroxide radical, which could undergo either a direct oxidative cleavage to give **6** or further reduction with Et_3B followed by excluding the cyano moiety to furnish diketone **7**.[7a]



Given that upon exposure to air or oxygen reactant **4** would suffer a significant loss in forming undesired products, attention was then paid to radical initiators which could work under inert gas atmosphere. A conventional radical initiator azobisisobutyronitrile (AIBN) under N_2 was first attempted (entry 6), but results were rather disappointing because a low conversion rate (32%) was observed even after reaction time was prolonged over 96 h. Reaction with *tert*-butyl hydroperoxide (TBHP) was then performed (entry 7), but the desired product, again, was obtained in low yield along with most of the starting material recovered intact.[8] However, to our delight, when the same reaction was conducted under catalysis with tetrabutylammonium iodide (TBAI, 20 mol %),[9] the yield was substantially improved up to 86% in 1 h though another side product **8** was detected in ca. 10% yield (entry 8).[10] On the basis of these encouraging results, an in-depth investigation on the above catalytic system was then carried out. Finally, we found that lowering both oxidant TBHP and reaction concentration to 1.1 equiv and 0.03 M, respectively, allowed for clean preparation of product **5** in 95% yield. As such, TBHP (1.1 equiv)/TBAI (20 mol %)/PhH (0.03 M) was considered the reaction system of choice and thus applied to an array of substrates

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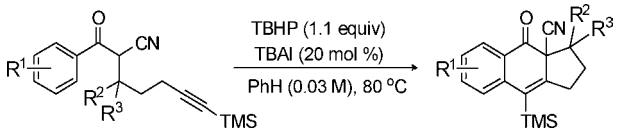
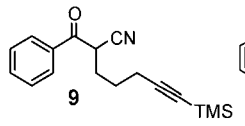
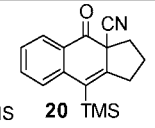
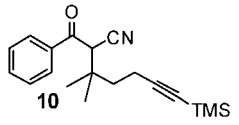
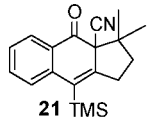
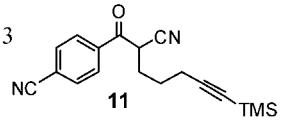
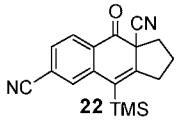
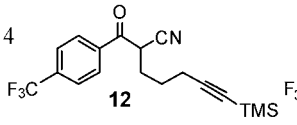
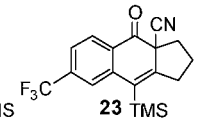
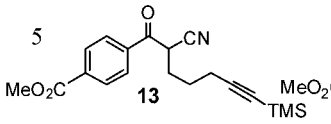
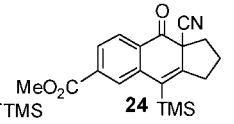
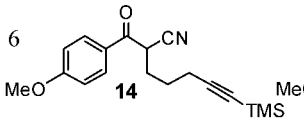
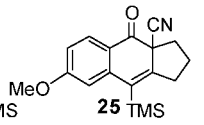
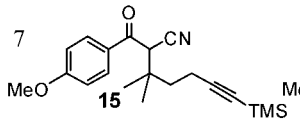
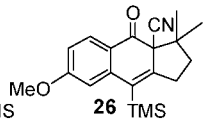
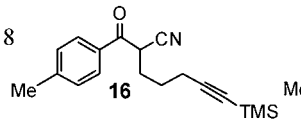
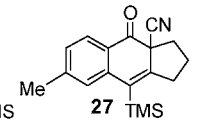
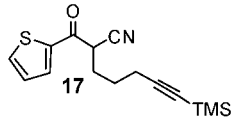
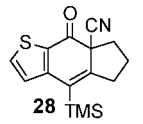
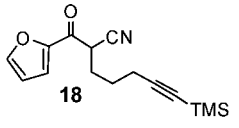
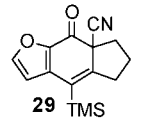
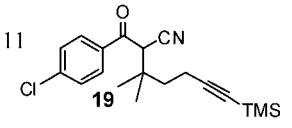
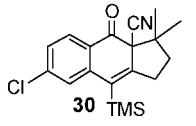
Table 2. Tandem Annulation of Various α-Cyano α-TMS-Capped Alkynyl Aryl Ketones



entry	substrate	product	yield (%)[a]
1			85[b]
2			96[c]
3			90[b]
4			98[b]
5			93[b]
6			72[b]
7			94[c]
8			91[b]
9			95[b]
10			85[b]
11			95[c]

[a] Isolated yield. [b] Reaction completed in 1 h. [c] Reaction completed in 30 min.

with greater structural diversity. As listed in Table 2, not only the generality of the methodology was attested but also a series of complex tricyclic compounds **20**–**30** became accessible. All substrates were readily prepared via the modified Knoevenagel condensation of commercially available arylacetonitrile with 5-(trimethylsilyl)-4-pentan-1-al in the presence of Hantzsch ester as a mild reducing agent and L-proline as a base in excellent yields,[11] with the exception that substrates **10**, **15**, and **19** were synthesized in a two-step sequence, involving Knoevenagel condensation and 1,4-conjugate addition, in good yields. The above synthetic procedures are detailed in the Supporting Information. In the current cases examined, the corresponding tricyclic products were obtained in high to excellent yields (85–98%) under optimized reaction conditions; however, while a strong electron-donating methoxy substituent at the para position was introduced (i.e., **14**), the cyclization product **25** was produced in moderate yield (72%) (Table 2, entry 6). An explanation could be that during the second [4 + 2] annulation, ring closure might be somewhat hampered, presumably due to a high delocalizing electron density bestowed with the methoxy group, thus rendering the formation of product slightly unfavorable. Nevertheless, as a *gem*-dimethyl group was installed at the β position to the ketone carbonyl, compound **15** thus formed could facilitate the cyclization process dramatically under similar reaction conditions, giving desired product **26** in excellent yield (94%) in less than 30 min (entry 7). These remarkable phenomena, enhancing reaction rate and/or yield by a *gem*-dimethyl group, were also observed with β-dimethyl substrates **10** (96%, 30 min vs **9** (85%, 1 h)) and **19** (95%, 30 min vs **4** (95%, 1 h)), suggesting that the Thorpe–Ingold effect[12] might play an important role in the current radical cascade by forcing an initial α-keto radical species to adopt a correct puckered conformation, ready for the subsequent [4 + 1] annulation, resulting in acceleration of the reaction rate; however, whether this process is a rate-limiting step remains to be determined in that mechanistically, four activation-energy barriers might exist along the reaction course.

The mechanistic rationale for the titled system is depicted in Scheme 2 using substrate **4** as a typical example. The cascade process is proposed to be initiated with abstracting H-atom, α to both cyano and carbonyl groups, by the free radical species *t*-BuO$^{\bullet}$ or *t*-BuOO$^{\bullet}$ generated by a catalytic cycle of oxidants TBHP and I_2. The initial α-keto radical intermediate A thus formed might undergo the first intramolecular 5-*exo*-*dig* cyclization to produce the vinyl radical intermediate B, by which the ensuing 6-*endo*-*trig* addition, giving rise to a cyclic pentadienyl

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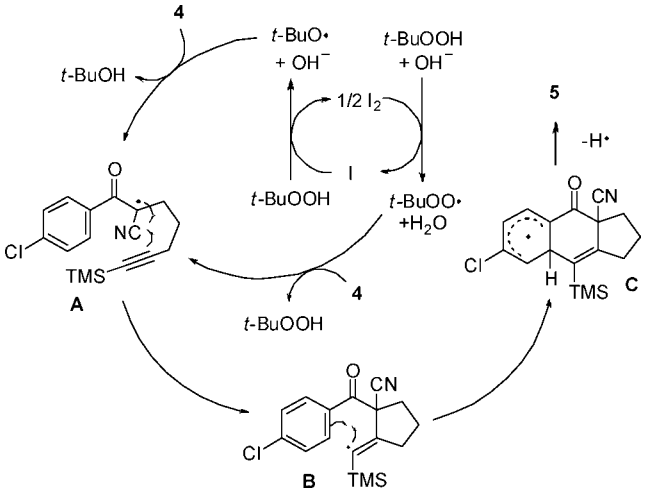
Scheme 2. Proposed Mechanism for the Intramolecular Tandem Cyclization Process



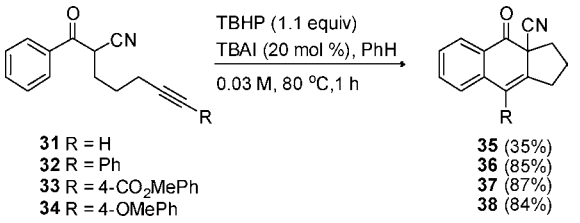
radical C, followed by aromatic homolytic substitution could occur to afford rearomatization product **5**.[13]

To clarify the role of the TMS group, substrate **31** (Scheme 3), a TMS-free counterpart of **9** (Table 2, entry 1), was synthesized for comparison. Upon treatment with the standard reaction conditions, the corresponding product **35** was merely obtained in 35% yield. As compared to product **20** formed in 85% yield from **9**, the results strongly suggested that the vinyl radical intermediate resulting from 5-*exo*-*dig* cyclization should be sufficiently stabilized by the TMS group to promote the ensuing [4 + 2] cycloaddition. Along this line, compounds **32**–**34**, replacing the TMS moiety with the phenyl group or its *para*-substituted analogues intended to provide the similar stabilizing force, were further prepared. As a result, irrespective of the stereoelectronic nature of the *para* substituent, all reactions proceeded in a predictable manner to afford the corresponding products **36**–**38** in high yields (84–87%) in 1 h,

(13) (a) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803. (b) Vaillard, S. E.; Schulte, B. In *Modern Arylation Methdods*; Ackermann, L., Eds.; Wiley-VCH: Weinheim, 2009; Chapter 13. (c) Vaillard, S. E.; Studer, A. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; John Wiley&Sons: New York, 2012; Chapter 37.

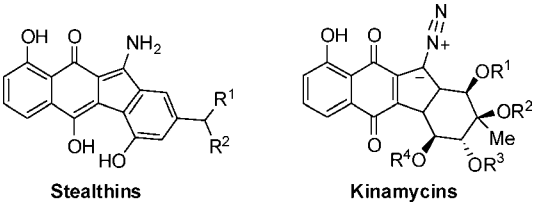
(14) (a) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *Org. Lett.* **2002**, *4*, 3659. (b) Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499.

Scheme 3



demonstrating that in addition to TMS, coupling with the other appropriate functionality at the terminal alkynyl unit to stabilize the vinyl radical species is feasible, thus broadening the synthetic utility of this newly developed method.

In summary, an intramolecular radical cascade of the α-cyano-TMS/aryl-capped alkynyl aryl alkyl ketones, promoted by oxidant TBHP under catalysis with TBAI, has been developed, culminating in the construction of a variety of [6,6,5] tricyclic frameworks containing a high level of functionalization efficiently. The methodology is currently under active investigation to expand its scope and is also extended to the synthesis of naturally occurring products, such as stealthins and kinamycins, bearing the tetracyclic benzo[*b*]fluorine skeletons with a broad spectrum of antibiotic properties.[14]



Acknowledgment. We are grateful to the National Health Research Institutes and National Science Council of Taiwan (NSC-100-2113-M-400-002; NSC-101-2113-M-400-003-MY2) for financial support.

Supporting Information Available. Experimental procedures, full characterization of new products, and copies of NMR and X-ray spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.