ORGANIC LETTERS

2010
Vol. 12, No. 19
4368−4371

Rapid Formation of Hindered Cores Using an Oxidative Prins Process

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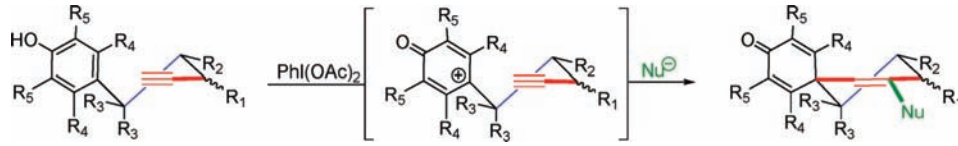
Received August 7, 2010

ABSTRACT



An unprecedented oxidative Prins transformation on phenol derivatives mediated by a hypervalent iodine reagent has been developed. This method allows a rapid access to highly substituted compact systems present in several natural products via a carbon-based addition on an aromatic core. Substitution at each ring position has been demonstrated, enabling synthesis of molecules with up to two contiguous quaternary carbon centers in good yield.

The well-known Prins transformation[1] was first reported by Kriewitz.[2] The reaction involves addition of an oxonium species to an alkene or an alkyne followed by capture of a nucleophile or elimination of hydrogen. Since there are several competing reaction pathways, it is important to control the reactivity of species **3** to generate only the desired product (Figure 1).

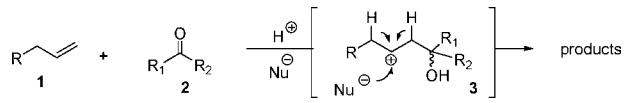


Figure 1. Prins transformation.

One control method was proposed by Overman[3] et al. in the famous Prins−pinacol tandem process. This method considerably reduces the formation of byproducts from intermediate **3** and often forms an efficient key step in the synthesis of complex natural products. Our own interest in oxidative dearomatization of electron-rich aromatics involving carbon-based nucleophiles[4] led us to question whether an oxidative variant of the Prins process could be initiated by oxidative activation of a phenol. Electron-rich aromatic compounds such as phenols and their derivatives normally react as nucleophiles. However, an oxidative activation[5,6] can transform these compounds into highly reactive electrophilic species such as **5**, which may be intercepted with appropriate nucleophiles. This reversal of reactivity may be thought of as involving "aromatic ring umpolung".[4] The phenoxonium ion **5** could be trapped by an intramolecular π bond via a chairlike transition state, leading to a spiro-

(1) (a) Prins, H. J. *Chem. Weekblad* **1919**, *16*, 64, 1072, 1510. (b) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505.

(2) (a) Kriewitz, O. *Ber.* **1899**, *32*, 57.

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(4) (a) Bérard, D.; Giroux, M. A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, 7537. (b) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629. (c) Sabot, C.; Commare, B.; Nahi, S.; Duceppe, M. A.; Guérard, K. C.; Canesi, S. *Synlett* **2008**, 3226. (d) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039. (e) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (f) Guérard, K. C.; Chapelle, C.; Giroux, M. A.; Sabot, C.; Beaulieu, M. A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756. (g) Guérard, K. C.; Sabot, C.; Beaulieu, M. A.; Giroux, M. A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893.

10.1021/ol101851z
Published on Web 09/02/2010

dienone species **6** similar to the previous Prins intermediate **3** (Figure 2).

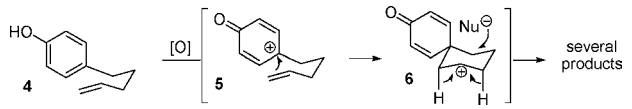


Figure 2. Oxidative Prins process.

An indication of how the formation of the corresponding phenol activation can be achieved is apparent in the work of Kita,[7] who has demonstrated that phenols react under the influence of hypervalent iodine reagents[8] such as (diacetoxyiodo)benzene (DIB), an environmentally benign and inexpensive reagent. This reaction is best performed in solvents such as hexafluoroisopropanol (HFIP).[7k]

As expected, activation of phenol **4** leads to a mixture of products representing the different plausible pathways beginning with intermediate **6**.[9] To limit the formation of side products, the reaction was investigated using a free alkyne moiety as the nucleophile. It was rationalized that the geometry of the strained half-chair species **8** would strongly favor nucleophile capture, leading to a spiro[5.5]undecanyl core **9**. This valuable bicyclic system is found in natural products such as laurencenone B[10] and platencin[11] (Figure 3).

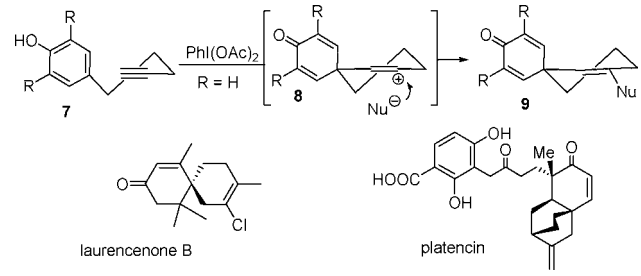
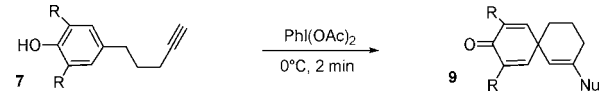


Figure 3. Formation of spiro[5.5]undecanyl cores.

The strain generated by the transient sp-hybridized carbon in species **8** rendered the intermediate highly electrophilic and enabled it to react with weakly reactive nucleophiles, including some normally used as inert solvents such as HFIP,[7k] dichloromethane (DCM) (as a chloride donor),[12] trifluoroacetic acid (TFA), and benzene. This last example can be considered as a tandem oxidative Prins/Friedel−Crafts process, demonstrating the potential utility of this strategy for further domino applications. A summary of experiments is presented in Table 1.

Table 1. Nucleophile Additions



entry	R	solvent	Nu	yield (%)
a	H	HFIP	$OCH(CF_3)_2$	61
b	H	HFIP/DCM	Cl	57
c	Br	HFIP/DCM	Cl	73
d	H	TFA	$OCOCF_3$	62
e	H	HFIP/PhH	Ph	50

It appears that all of the heteronucleophiles react similarly. In the case of compound **9d**, the fragile enol-ether is rapidly

(5) (a) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (b) Swenton, J. S.; Callinan, A.; Chen, Y.; Rohde, J. J.; Kearns, M. L.; Morrow, G. W. *J. Org. Chem.* **1996**, *61*, 1267. (c) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E. M. *Tetrahedron Lett.* **1998**, *39*, 4667. (d) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (e) Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E. M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (f) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. (g) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. (h) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193. (i) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336. (j) Quideau, S.; Pouységu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113. (k) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175. (l) Honda, T.; Shigehisa, H. *Org. Lett.* **2006**, *8*, 657. (m) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem.* **2007**, *119*, 4016. (n) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (o) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. (p) Giroux, M. A.; Guérard, K. C.; Beaulieu, M. A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871. (q) Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 4736. (r) Quideau, S.; Lyvinec, G.; Marguerit, B. K.; Ozanne-Beaudenon, A.; Bufeteau, T.; Cavagnat, D.; Chenede, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (s) Liang, H.; Ciufolini, M. A. *Org. Lett.* **2010**, *12*, 1760.

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(7) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5854. (d) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481. (e) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698. (f) Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y. *Chem. Commun.* **1999**, 469. (g) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75. (h) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (i) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (j) Dohi, T.; Itob, M.; Yamaokaa, N.; Morimotoa, K.; Fujiokab, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (k) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

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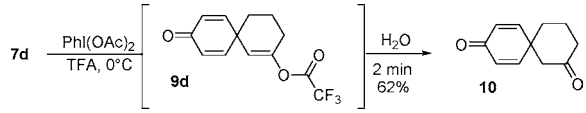
(9) The presence of a mixture of isomers providing from an elimination and a nucleophilic addition has been verified by mass spectroscopy.

(10) Kennedy, D. J.; Selby, I. A.; Thomson, R. H. *Phytochemistry* **1988**, *27*, 1761.

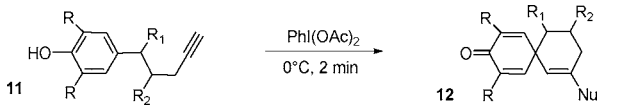
hydrolyzed during workup into the corresponding ketone **10**; this transformation is formally an oxidative Claisen/Dieckmann-type condensation (Scheme 1).

Scheme 1. Oxidative Claisen/Dieckmann Process



To determine the scope and limitations of this novel transformation, various substituents were introduced on the lateral chain to generate more elaborate bicyclic systems. A summary of experiments performed using 1- or 2-substituted phenols is presented in Table 2.

Table 2. Effects of Substituents at Positions 1 and 2

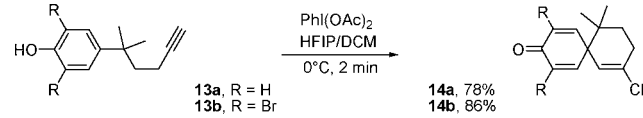


entry	R	R_1	R_2	Nu	yield (%)
a	H	Me	H	$OCH(CF_3)_2$[i]	71
b	H	H	Me	$OCH(CF_3)_2$[i]	59
c	H	Me	H	$OCOCF_3$[ii]	83
d	H	H	Me	$OCOCF_3$[ii]	57
e	H	Me	H	Cl[iii]	79
f	H	H	Me	Cl[iii]	60
g	H	$CH_2CH{=}CH_2$	H	Cl[iii]	81
h	Br	PH	H	Cl[iii]	74

[i] HFIP used as solvent. [ii] TFA used as solvent. [iii] Mixture of DCM/HFIP, 9:1, used as solvent.

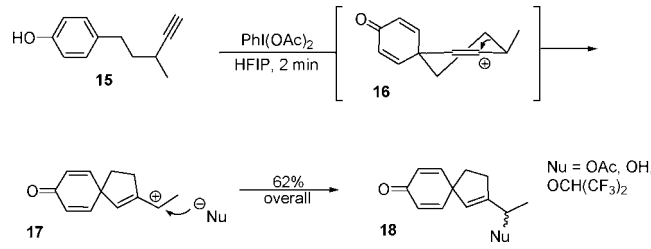
Substitution at position 2 (R_2) seems to have no influence on the yield of this reaction. However, the presence of bromine atoms in the *ortho* positions or more importantly a substituent in position 1 (R_1) clearly increases the yield. This result could be rationalized by considering that a common limitation of oxidative processes is competitive hydrogen elimination during formation of the phenoxonium ion **5**, leading to an easily polymerizable quinone methide. The presence of only one hydrogen atom would limit this side reaction. In addition, the weak electron-donating effect of the substituent in position 1 could slightly increase the stability of the phenoxonium ion, favoring nucleophilic addition. These results suggest the potential for constructing highly hindered cores containing contiguous quaternary carbon centers. Indeed, the elaboration of such challenging systems is often restricted by the steric hindrance of the first quaternary carbon center. The introduction of two substituents in position 1 would help stabilize the phenoxonium ion generated during the umpolung activation and would create a contiguous spiro quaternary center. The difficulty normally associated with the synthesis of such frameworks would turn into an advantage. To verify this hypothesis, a second substituent was introduced at position 1 (Scheme 2).

Scheme 2. Contiguous Quaternary Carbon Center Formation



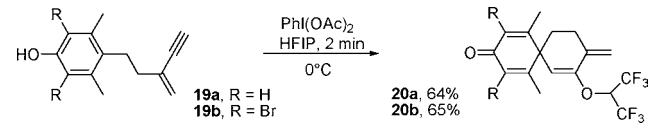
We were pleased to observe the formation of the desired compounds in good yields considering the architecture produced. We have also investigated the effect of a methyl group in position 3, and the formation of a spiro[4.5]decanyl core **18** via a Wagner−Meerwein transposition process has been observed. The electron density provided by the methyl group in position 3 probably favored a ring contraction process on the species **16**. The corresponding carbocation **17** was trapped by various nucleophiles present in the medium to afford compound **18** (Scheme 3).

Scheme 3. Ring Contraction



This transposition may be easily avoided by introducing a methylene group in position 3; indeed, the sp^2 hybridization in this position now retards the ring contraction process in favor of nucleophilic capture. To produce a potential precursor of laurencenone B **10**, methyl groups were introduced at the *meta* positions (Scheme 4).

Scheme 4. Substituent in Position 3



(11) Jayasuriya, H.; Herath, K. B.; Zhang, C.; Zink, D. L.; Basilio, A.; Genilloud, O.; Teresa Diez, M.; Vicente, F.; Gonzalez, I.; Salazar, O.; Pelaez, F.; Cummings, R.; Ha, S.; Wang, J.; Singh, S. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 4684.

(12) (a) Kropp, P. J.; McNeely, S. A.; Davis, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 6907. (b) Miyamoto, K.; Shiro, M.; Ochiai, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8931. The nucleophilic capture of **9** by a chloride can sometimes be accompanied by a small amount (~5%) of HFIP capture.

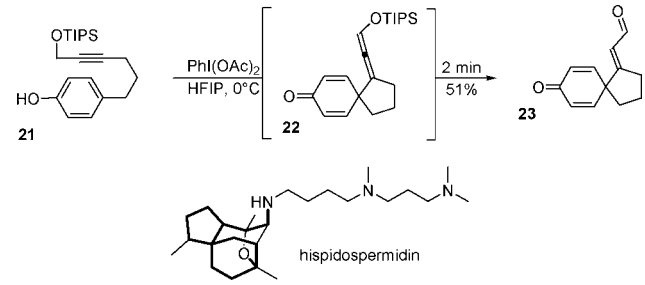
After having placed substituents at all positions on the aromatic core and the lateral chain, the free alkyne moiety was functionalized. The introduction of a protected methylene alcohol at this position resulted in the formation of the spiro[4.5]decanyl system **23**. This can be attributed to the steric bulk of the substituent forcing the π bond to react in a 5-exo-dig mode instead of the standard 6-endo-dig observed with free alkynes. The formation of compound **23** could occur via hydrolysis of a potential allene intermediate **22** or more probably through a pinacol-type process. A good diastereoselectivity (9:1)[13] in favor of the (*E*)-isomer was observed. This new selectivity of the alkyne functionality during the oxidative Prins transformation presents novel opportunities such as the facile construction of the subunit present in the natural product hispidospermidin[14] (Scheme 5).

In summary, a new oxidative Prins process has been developed that enables rapid access to functionalized and highly hindered spirocyclic compounds such as those present in numerous natural products. This method is an efficient means of producing two contiguous quaternary carbon centers. Ongoing investigations of this process and potential applications will be disclosed in due course.

(13) The ratio has been determined by NMR 300 MHz.

(14) Yanagisawa, M.; Sakai, A.; Adachi, K.; Sano, T.; Watanabe, K.; Tanaka, Y.; Okuda, T. *J. Antibiot.* **1994**, *47*, 1.

Scheme 5. Formation of a Spiro[4.5]decanyl Core



Acknowledgment. We would like to acknowledge the donors to the American Chemical Society Petroleum Research Fund (ACS PRF) for supporting this research. We are very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), and Boehringer Ingelheim (Canada) Ltd. for their financial support.

Supporting Information Available: Experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101851Z