ORGANIC LETTERS

2009
Vol. 11, No. 20
4756−4759

An Unprecedented Oxidative Wagner−Meerwein Transposition

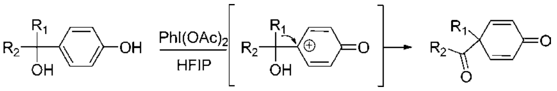
Kimiaka C. Guérard, Clément Chapelle, Marc-André Giroux, Cyrille Sabot, Marc-André Beaulieu, Nabil Achache, and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8, Québec, Canada

canesi.sylvain@uqam.ca

Received August 27, 2009

ABSTRACT



An oxidative Wagner−Meerwein transposition involving different functionalities mediated by a hypervalent iodine reagent has been accomplished. The strategy fits within the concept of "aromatic ring umpolung" and allows rapid access to highly functionalized cores.

One of the most remarkable transformations in organic synthesis is probably transposition. Indeed, this process allows the transformation of a simple structure into a variety of more complex motifs. The Wagner−Meerwein and pinacolic transpositions[1] are among the most well-known of these rearrangements. Moreover, electron-rich aromatic compounds, such as phenols and their derivatives, normally react as nucleophiles. However, an oxidative activation[2−4] can transform these aromatics into very reactive electrophilic species **2**, which may be intercepted with appropriate nucleophiles in synthetically useful yields. An indication of how this objective can be achieved is apparent in the work of Kita,[2] who has shown that phenols may be activated under the influence of hypervalent iodine reagents such as iodobenzene diacetate (DIB), an environmentally benign and inexpensive reagent. This reaction is generally best performed in solvents such as hexafluoroisopropanol (HFIP).[2] If one considers the behavior of the electrophilic species **2**, this reversal of reactivity may thus be thought of as involving "aromatic ring umpolung".[5,6] This concept provides new strategic opportunities in synthetic chemistry, by extension of several well-known reactions in aliphatic chemistry to aromatic chemistry. An oxidative extension of a transposition could lead rapidly to a plethora of applications in total synthesis. In this paper, we illustrate an extension to the Wagner−Meerwein rearrangement to phenols that takes place via an oxidative process (Figure 1).

As an initial investigation, we decided to test the feasibility of an oxidative transposition. In this purpose, the corresponding phenols **4** have been oxidized to generate the

---

[1] (a) Fittig, R. *Justus Liebigs Ann. Chem.* **1860**, *114*, 54. (b) Wagner, G. *J. Russ. Chem. Soc.* **1899**, *31*, 690. (c) Meerwein, H. *Justus Liebigs Ann. Chem.* **1914**, *405*, 129.

[2] (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.

[3] (a) Pelter, A.; Drake, R. A. *Tetrahedron Lett.* **1988**, *29*, 4181. (b) Quideau, S.; Looney, M. A.; Pouységu, L. *J. Org. Chem.* **1998**, *63*, 9597. (c) Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065. (d) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318. (e) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, *24*, 3759. (f) Bérard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238. (g) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553. (h) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A. M.; Miqueu, K.; Sotiropoulos, J. M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552. (i) Bérard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, 1076. (j) Pouységu, L.; Marguerit, M.; Gagnepain, J.; Lyvinec, G.; Eatherton, A. J.; Quideau, S. *Org. Lett.* **2008**, *10*, 5211. (k) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299, and citations therein. (l) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (m) Quideau, S.; Lyvinec, G.; Marguerit, Bathany, K.; Ozanne-Beaudenon, A.; Bufeteau, T.; Cavagnat, D.; Chenede, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605.

10.1021/ol902000j CCC: $40.75

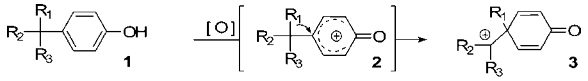


Figure 1. Oxidative migration.

electrophilic species **5**. This latter promotes the desired rearrangement leading to compounds **6** in useful yields (33−67%). Formation of compound **4** is easily obtained in high yield by addition of an excess of allyl Grignard on the corresponding 4-hydroxyphenones. Allyl groups have been chosen because they are known to be very good migrating groups involving a potential concerted mechanism during the transition state. It should be noted that the direct migration of the allyl group is not excluded (Figure 2).

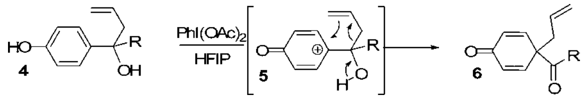
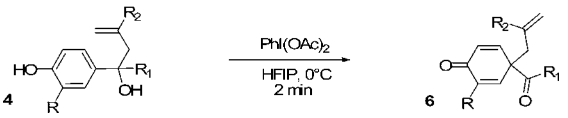


Figure 2. Oxidative allylic migration.

An important aspect of this strategy is the ability to transform quickly an inexpensive and simple phenol into a highly functionalized core containing a prochiral dienone, a quaternary carbon center connected to several sp^2 carbons, and spectator functionalities could be present on the side chain. To exemplify this transformation, different phenols containing an allyl group have been oxidized. A summary of representative experiments appears in Table 1.

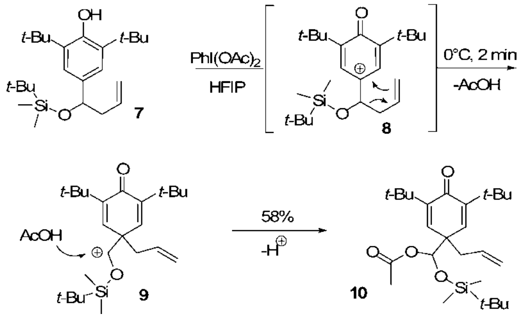
Table 1. Oxidative Allylic Transposition



entry	R	R_1	R_2	yield
a	H	Me	H	62
b	H	$CH_2CH{=}CH_2$	H	67
c	Me	Me	H	63
d	H	Me	Me	37
e	H	CH_2OTBS	H	33

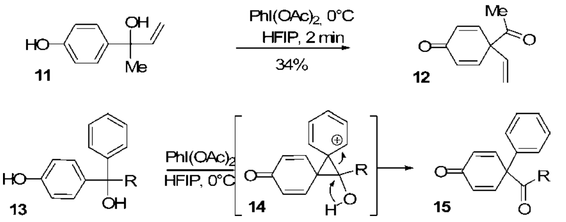
In addition, a noteworthy transformation is observed by oxidation of the silicon-ether **7** leading to the acetal **10** in 58% yield. Indeed, the alkene moiety present in the side chain would react with the potential cation **8**, and a C−C bond fragmentation would lead to intermediate **9** that would be trapped by the acetic acid released during the reaction to afford **10**. This transformation is similar to an oxidative pinacol/acetalization tandem process. It should be noted that such acetal functionality has never been reported as of this writing. A potential mechanism is described in Scheme 1.

Scheme 1. Oxidative Transposition−Acetal Tandem Process



To broaden the scope of this reaction, other potential migrating groups have been tested with sp^2 carbons such as an alkene or an aryl. These groups are easily introduced by a 1−2 addition on the corresponding ketone. The formation of the corresponding dienone **15** is observed, probably via the formation of an arenium intermediate **14**. Obtaining a structure such as **12** or **15** represents a synthetic challenge due to the complexity associated with generating a quaternary carbon center connected to four sp^2 carbons. Indeed, the formation of such architecture using conventional chemistry could become problematic (Scheme 2).

Scheme 2. sp^2 Carbon Migration



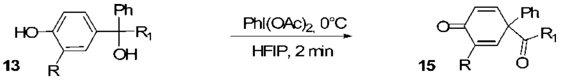
To exemplify this transformation, different phenols containing an aryl group have been oxidized. The skeleton

---

(4) (a) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (b) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E. M. *Tetrahedron Lett.* **1998**, *39*, 4667. (c) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (d) Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E. M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (e) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (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) Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493. (j) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336. (k) Quideau, S.; Pouységu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113. (l) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175. (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**, 4299. (p) Giroux, M. A.; Guérard, K. C.; Beaulieu, M. A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871.

generated should have different applications in total synthesis, due to the numerous natural products containing such core, such as the *Amaryllidaceae* alkaloids family.[7] A summary of representative experiments appears in Table 2.

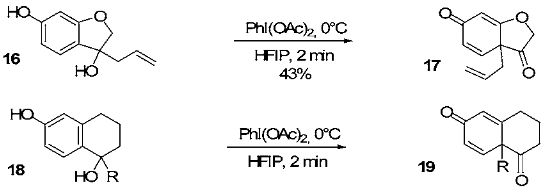
Table 2. Migration of Aryl Groups



entry	R	R_1	yield
a	H	Me	51
b	Me	Me	34
c	H	Et	35

This strategy can also be used with bicyclic phenols to produce the corresponding dienone skeleton (Scheme 3).

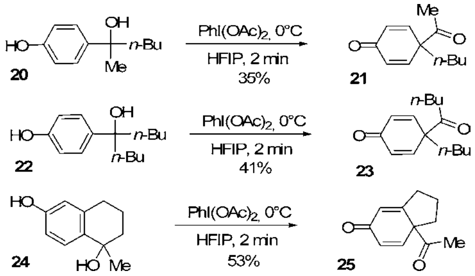
Scheme 3. Oxidation of Bicyclic Phenols



entry	R	Yield
a	$CH_2\text{-}CH{=}CH_2$	**43**
b	Ph	**54**

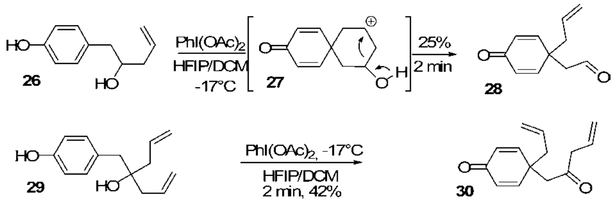
To explore the scope and limitations of this reaction, we proceeded to extend the feasibility of this rearrangement to simple alkyl groups. In this purpose, oxidations of acyclic and bicyclic phenols have been accomplished. As expected, during the oxidation of compound **20** the migration of the butyl group is very predominant; only a small amount of methyl migration is observed (~5%). In addition, oxidation of phenol **22** leads to compound **23**, in 41% yield. It should be noted that this oxidative process seems to occur as a regular rearrangement applicable to a large scope of aryl, allyl, and alkyl groups. Indeed, the same rules as the ones applying to a conventional Wagner−Meerwein transposition are observed. In addition, an oxidation of compound **24** produces a noteworthy ring contraction leading to **25** in 53% yield. These results demonstrate the large potential of this novel transformation and its potential application in synthesis (Scheme 4).

Scheme 4. Migration of Alkyl Groups



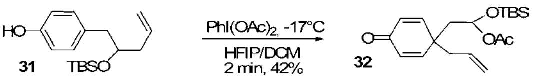
The reaction with allyl groups can be extended to compounds **26** and **29**, via an unprecedented 1,3-allyl shift, probably due to a concerted mechanism involving an intermediate such as **27**. This transformation could be assimilated to an unreported homo-Wagner−Merweein process. This strategy leading to such cores could be helpful to produce rapidly elaborated structures (Scheme 5).

Scheme 5. Homo-Wagner−Meerwein Transposition



This transformation with compound **26** occurs in low yield; further investigation has demonstrated that the corresponding aldehyde **28** was not very stable in these conditions. To solve this problem, the corresponding aldehyde generated in situ has been transformed into a more stable functionality. Indeed, the transposition/acetalization process described in Scheme 2 has been used on compound **31** to produce a mixed acetal **34** in 42% yields. This later is associated with a small amount of aldehyde **28** (5−10%) (Scheme 6).

Scheme 6. Oxidative 1,3-Allyl Shift



To broaden the scope of this novel transposition, the allylic segment has been substituted by a propargylic group.

---

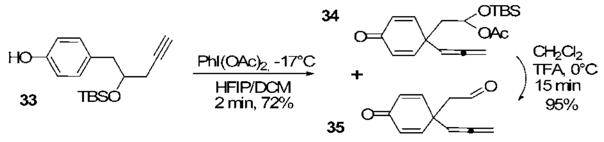
(5) The concept of "umpolung" chemistry has been discovered by E. J. Corey and D. Seebach: (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (b) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239.

(6) (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.

(7) (a) Ochi, M.; Otsuki, K.; Nagao, K. *Bull. Chem. Soc. Jpn.* **1976**, 3363. (b) Likhitwitayawuld, K.; Angerhofer, C. K.; Chai, H.; Pezzuto, J. M.; Cordell, G. A.; Ruangrungsi, N. *J. Nat. Prod.* **1993**, *56*, 1331. (c) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 107. (d) Abdel-Halim, O. B.; Morikawa, T.; Ando, S.; Matsuda, H.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 1119. (e) Szlavik, L.; Cyuris, A.; Minarovits, J.; Forgo, P.; Molnar, J.; Hohmann, J. *Plant Med.* **2004**, *70*, 871. (f) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 111.

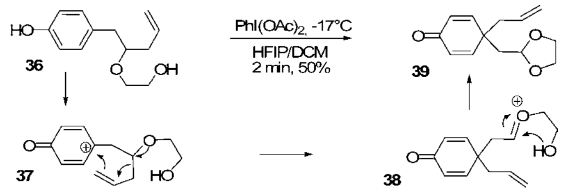
Oxidation of compound **33** produces the desired allenic moiety with a noteworthy global yield of 72% and in a ratio close to (3/2) between the acetal **34** and the aldehyde **35**. Treatment of compound **34** with TFA leads quantitatively to the aldehyde **35**. This process seems to occur more efficiently with a propargylic group than an allyl group. This aspect could be rationalized by the linear geometry of the sp carbon center that would be more oriented to interact with the phenoxonium ion generated (Scheme 7).

Scheme 7. Formation of Allenic Moiety



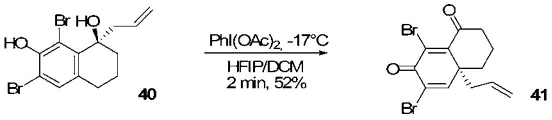
We have also been interested to trap the corresponding oxonium generated on the side chain with an intramolecular nucleophile that does not need the presence of acetic acid in the medium. The oxidation of compound **36** leads to the acetal **39**. An interesting aspect of this reaction is the spectacular rearrangement observed during the umpolung activation. Indeed, a simple phenol containing an ether functionality is redesigned in only one step into a highly elaborated core containing several functionalities present on almost each carbon (Scheme 8).

Scheme 8. Oxidative Transposition/Acetalization Tandem Process



In addition, this transposition can be accomplished on the bicyclic phenol **40** to produce the dienone **41** in 52% yield. The introduction of bromines in *ortho* position is necessary to force the allyl group during the oxidative process to react only in *para* position. Moreover, we suppose that the migration of the allyl group should occur stereospecifically with a retention of configuration, due to the concertness of the mechanism involved (Scheme 9).

Scheme 9. Carbocyclization−Fragmentation Process



In summary, an unprecedented and oxidative transposition process allows a rapid access to highly functionalized synthons containing a dienone, a quaternary carbon center directly connected to several sp^2 carbons. This transformation provides new strategic opportunities in the chemical synthesis of substances and results in ongoing investigations; their applications will be disclosed in due course.

Acknowledgment. Acknowledgment is made to the Donors of the American Chemical Society Petroleum Research Fund (ACS PRF) for support of this research. We are also very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), the provincial government of Quebec (FQRNT), and to Boehringer Ingelheim (Canada) Ltd. for their financial support.

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

OL902000J