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Dehydrative Fragmentation of 5-Hydroxyalkyl-1*H*-tetrazoles: A Mild Route to Alkylidenecarbenes

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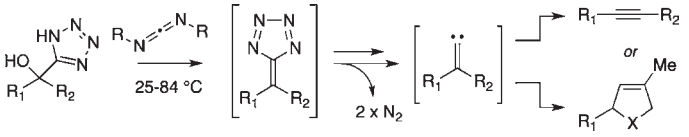
ABSTRACT



The development of a mild, base-free method for the generation of alkylidenecarbenes is reported. Treatment of 5-hydroxyalkyl-1*H*-tetrazoles with carbodiimides generates products arising from the 1,2-rearrangement or [1,5]-C−H bond insertion of a putative alkylidenecarbene. Formation of this divalent intermediate is proposed to occur by way of a tetraazafulvene, which undergoes extrusion of 2 mol of dinitrogen. Details of this methodology, its application to the synthesis of combretastatin A-4, and an improved route to 5-hydroxyalkyl-1*H*-tetrazoles are described.

1*H*-Tetrazoles have long been recognized as metabolically stable bioisosteres of the carboxylate group for which reason they have found widespread application in medicinal chemistry.[1] Our interest in these nitrogen-rich heterocycles, however, stems from their chemical instability[2,3] and attendant potential as precursors of alkylidenecarbenes: transient, electron-deficient species, which undergo a number of synthetically valuable reactions, including [1,2]-rearrangement, ylide formation, alkene cyclopropanation and [1,5]-C−H bond insertion.[4] Over the past decade, we have studied the latter transformation as a means to access *O*- and *N*-heterocycles and natural products that encompass these ring systems.[5]

Synthetic potential notwithstanding, the practical value of alkylidenecarbenes remains limited by a deficiency of methods for their generation under nonbasic conditions.[6] Although a number of noteworthy solutions to this issue have been reported, including the thermolysis of epoxyaziridinyl imines[7] and addition of "soft" nucleophiles to alkynyl(phenyl)iodonium salts,[8] the continued development of new methods appears to be warranted. In this context, we were intrigued by a rarely cited report from

(1) For reviews of the medicinal chemistry of 1*H*-tetrazoles, see: (a) Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd.* **2007**, *43*, 1. (b) Herr, J. R. *Bioorg. Med. Chem.* **2002**, *10*, 3379.

(2) In this context, tetrazoles play a key role in many modern high-energy density materials (HEDM): Klapötke, T. M., *Structure and Bonding (Berlin)*; Springer: Berlin/Heidelberg, Germany, 2007; Vol. 125, p 85.

(3) For a review of the thermal decomposition of tetrazoles, see: Lesnikovich, A. I.; Levchik, S. V.; Balabanovich, A. I.; Ivashkevich, O. A.; Gaponik, P. N. *Thermochim. Acta* **1992**, *200*, 427.

(4) For reviews of alkylidenecarbene chemistry and the Fritsch–Buttenberg–Wiechell (FBW) rearrangement, see: (a) Jahnke, E.; Tykwinski, R. R. *Chem. Commun.* **2010**, 3235. (b) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795. (c) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36* (6), 1164. (d) Taber, D. F. In *Methods of Organic Chemistry*, 4th ed.; Helmchen, G., Ed.; Georg Thieme Verlag: New York, 1995; Vol. E21, p 1127. (e) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274. (f) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383.

(5) (a) Wardrop, D. J.; Fritz, J. *Org. Lett.* **2006**, *8*, 3659. (b) Wardrop, D. J.; Bowen, E. G. *Chem. Commun.* **2005**, 5106. (c) Wardrop, D. J.; Zhang, W.; Fritz, J. *Org. Lett.* **2002**, *4*, 489. (d) Wardrop, D. J.; Zhang, W. *Tetrahedron Lett.* **2002**, *43*, 5389. (e) Wardrop, D. J.; Velter, A. I.; Forslund, R. E. *Org. Lett.* **2001**, *3*, 2261.

(6) For representative examples of alkylidenecarbene generation under strongly basic conditions, see: (a) Walsh, R. A.; Bottini, A. T. *J. Org. Chem.* **1970**, *35*, 1086. (b) Stang, P. J.; Mangum, M., G.; Fox, D., P.; Haak, P. *J. Am. Chem. Soc.* **1974**, *96*, 4562. (c) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673. (d) Green, M. P.; Prodger, J. C.; Sherlock, A. E.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3377. (e) Reference 5b.

(7) (a) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1994**, *35*, 8405. (b) Kirmse, W. *Eur. J. Org. Chem.* **1998**, 201.

(8) (a) Ochiai, M.; Kunishima, M.; Tani, S.; Nagao, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3135. (b) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93. (c) Feldman, K. S. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier Academic Press: London, 2004; Vol. 4, p 133. (d) Reference 5c.

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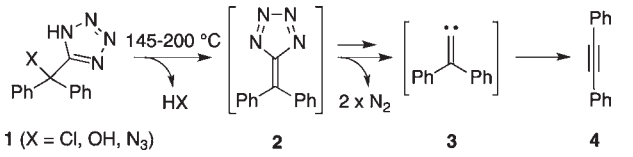
Behringer regarding the thermolysis and rearrangement of 5-hydroxy(diarylmethyl)-1*H*-tetrazoles and related derivatives **1** to form diarylalkynes **4** (Scheme 1).[9] In this case, dehydration of **1** (X = OH) was proposed to generate unstable tetraazafulvene intermediate **2** which undergoes conversion to the observed products through extrusion of 2 mol of dinitrogen and rearrangement of the resulting alkylidenecarbene **3**.[10,11]

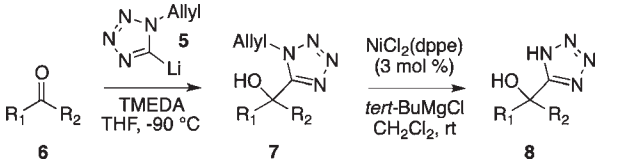
Scheme 1

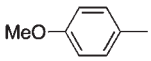
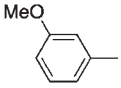
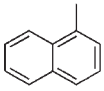
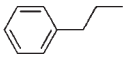
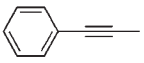


Here we report on our investigation of this unusual tetrazole reactivity manifold and the development of conditions that trigger the dehydration and fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles to form alkylidenecarbenes under exceptionally mild conditions. In addition to employing this methodology in the preparation of alkynes, diynes, triynes, and five-membered hetero/carbocycles, its application to the stereoselective total synthesis of combretastatin A4 (**18**) is also described.

Our study commenced with the development of a general method for the preparation of 5-hydroxyalkyl-1*H*-tetrazoles **7** (Table 1). While potentially available from cyanohydrins via cycloaddition with azide,[12] we sought to establish a more flexible route to these substrates that avoided the direct use of cyanide and azide-based reagents.[13] In this regard, we opted to adapt a two-step protocol reported by Satoh involving the addition of 1-benzyl-5-tetrazoyllithium to carbonyl electrophiles and subsequent de-*N*-benzylation.[14,15] Thus, treatment of ketones, ynones, and an aldehyde **6** with 1-allyl-5-tetrazoyllithium (**5**)[16] in THF at low temperature provided the desired alcohols **7** in excellent yield (Table 1).

Table 1. Preparation of 5-Hydroxyalkyl-1*H*-tetrazoles **8**



entry	R_1	R_2	**7** (yield %)[a]	**8** (yield %)[b]
1		Ph	**7a**, 90	**8a**, 99
2		Ph	**7b**, 87	**8b**, 99
3		Ph	**7c**, 93	**8c**, 98
4		Ph	**7d**, 99	**8d**, 99
5		Ph	**7e**, 90	**8e**, 99
6		Ph	**7f**, 96	**8f**, 99
7		Ph	**7g**, 92	**8g**, 32[c]
8	*n*-Pentyl	Ph	**7h**, 83	**8h**, 76[c]
9		Ph	**7i**, 99	**8i**, 99
10		H	**7j**, 78	**8j**, 89
11		Ph	**7k**, 99	**8k**, 99
12	*n*-Bu—	*n*-Bu—	**7l**, 70	**8l**, 50[c]

[a] Unless otherwise noted, isolated yield, after purification by flash chromatography on silica gel. [b] Unless otherwise noted, yield after aqueous workup; no further purification required. [c] Isolated yield, after purification by back extraction.

Efficient, direct de-*N*-allylation of the addition products **7** was now accomplished under Yamamoto's conditions,[17] by treatment with a combination of catalytic $NiCl_2$(dppe) and *tert*-BuMgCl in CH_2Cl_2 (Table 1). The ease with which the *N*-allyl groups are removed from **7** is notable, as cleavage of *N*-benzyl protecting groups from this type of substrate has previously proved problematic.[14a]

Turning our attention to the generation of alkylidenecarbenes **9**, we now opted to examine carbodiimide dehydrating agents as a means to access the putative tetraazafulvene intermediate since Behringer noted a single example of the use of DCC in mediating the decomposition of **1**. Gratifyingly, treatment of **8a** with a range of

(9) Behringer, H.; Matner, M. *Tetrahedron Lett*. **1966**, *24*, 1663.

(10) Tetraazafulvene intermediates have also been implicated in the Pb(IV)-mediated oxidation of 2-(tetrazol-5-yl)alkanoic acids: Fetter, J.; Nagy, I.; Giang, L. T.; Kajtár-Peredy, M.; Rockenbauer, A.; Korecz, L.; Czira, G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1131. See also (b) Scott, F. L.; Donovan, J.; O'Halloran, J. K. *Tetrahedron Lett*. **1970**, *28*, 4079.

(11) The mechanism by which nitrogen loss occurs in this case is, as yet, unknown.

(12) For an overview of this transformation, see: Wittenberger, S. J. *Org. Prep. Proced. Int*. **1994**, *26*, 499.

(13) For a complementary approach to alkylidenecarbenes from α-cyanomesylates, see: Cordonnier, R.; Van Nhien, A. N.; Soriano, E.; Marco-Contelles, J.; Postel, D. *Tetrahedron* **2010**, *66*, 736.

(14) (a) Satoh, Y.; Marcopulos, N. *Tetrahedron Lett*. **1995**, *36*, 1759. (b) Raap, R. *Can. J. Chem*. **1971**, *49*, 2139.

(15) For a review of the organometallic chemistry of tetrazoles, see: Voitekhovich, S. V.; Gaponik, P. N.; Koldobskii, G. I. *Russ. J. Org. Chem*. **2005**, *41*, 1599.

(16) Generated by *n*-BuLi-mediated deprotonation of 1-allyltetrazole, which is available in one step through the condensation of allylamine, sodium azide, and ethyl orthoformate: Gaponik, P. N.; Karavai, V. P.; Grigor'ev, Y. V. *Chem. Heterocycl. Compd*. **1985**, *11*, 1255.

(17) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Org. Chem*. **2002**, *67*, 7413.

carbodiimides, including DCC, EDC, and, most conveniently, diisopropylcarbodiimide (DIC), smoothly provided diphenylacetylene (**10a**) in excellent yield (Figure 1). In all cases but **8f** and **8l**, decomposition occurred at room temperature over the course of 24 h.

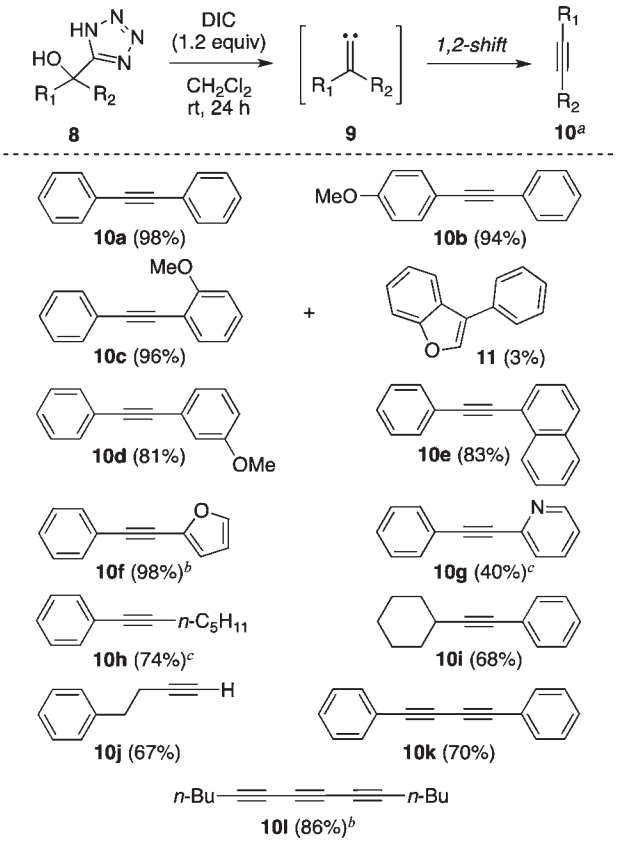


Figure 1. Dehydrative fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles: alkylidenecarbene 1,2-rearrangement. [a]Unless otherwise noted, isolated yield, after purification by flash chromatography on silica gel. [b]Reaction conducted in 1,2-dichloroethane at reflux: **10f** (5 min); **10l** (1 h). [c]EDC used in place of DIC for ease of purification.

That the onset of these reactions is accompanied by the generation of nitrogen gas appears to be consistent with the proposed mechanism. Encouragingly, this process displays considerable scope and offers access to symmetrical and nonsymmetrical alkynes (**10a**–**j**) as well as diynes (**10k**) and triynes (**10l**) in yields which compare favorably with the 1,2-rearrangement of other precursors, including 1,1-dihaloalkenes.[18] In addition to product **10c**, dehydration of *o*-anisole derivative **8c** also yielded traces (3%) of 3-phenylbenzofuran (**11**), which is believed to arise from carbene **9c** through competitive oxonium ylide formation and de-*O*-alkylation at the *o*-MeO substituent.[19] That pyridines are known to undergo ring opening in the presence of carbodiimides may account for the inefficiency observed during the formation of product **10g**.[20]

Given the success of the [1,2]-rearrangement process, we next sought to expand our methodology to include the [1,5]-C–H insertion manifold. In this case, substrates were purposely chosen with substituents known to have low migratory aptitude.[21] The requisite tetrazoles **12** (Figure 2) were prepared from the corresponding methyl ketones through the two-step sequence previously described. In all cases, the overall yield of these substrates compared favorably with those noted in Table 1.

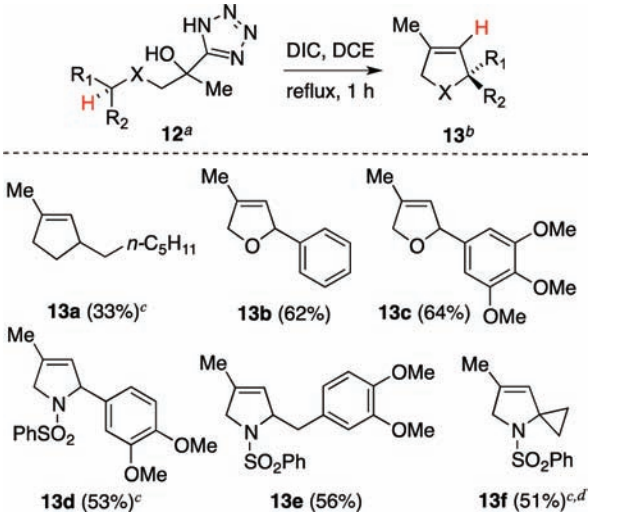


Figure 2. Dehydrative fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles: alkylidenecarbene [1,5]–C-H bond insertion. [a]For details of the preparation of substrates **12a**–**f**, see Supporting Information. [b]Isolated yields, after purification by flash chromatography on silica gel. [c]DCC used in place of DIC. [d]Isolated as an inseparable 5:4 mixture of [1,5]-C–H insertion and 1,2-rearrangement products.

While attempts to effect the decomposition of **12** at room temperature in the presence of DIC or DCC failed, conducting this reaction in 1,2-dichloroethane at reflux (84 °C) rapidly generated the desired insertion products **13** in reasonable yield. Significantly, the efficiency of these cyclizations compare favorably with that of other intramolecular alkylidenecarbene C–H insertion reactions.[22] While the low yield of cyclopentene **13a** arises, in part, from the volatility of this product, it may also reflect the increased bond dissociation energy of the target C–H

(18) For selected examples of alkyne formation through the 1,2-rearrangement of alkylidenecarbenes or their carbenoids, see: (a) Reference 6b. (b) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869. (c) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. (d) Eisler, S.; Tykwinski, R. R. *J. Am. Chem. Soc.* **2000**, *122*, 10736. (e) Reference 4b. (f) Reference 8a.

(19) Hari, Y; Kondo, R.; Date, K.; Aoyama, T. *Tetrahedron* **2009**, *65*, 8708.

(20) Wilchek, M.; Miron, T.; Kohn, J. *Anal. Biochem.* **1981**, *114*, 419.

(21) Wolinsky, J.; Clark, G. W.; Thorstenson, P. C. *J. Org. Chem.* **1976**, *41*, 745.

(22) For the preparation of **13b** (28–48%) via the C–H insertion of an alkylidenecarbene generated from 1,1-dihaloalkenes, see: Kunishima, M.; Hioki, K.; Tani, S.; Kato, A. *Tetrahedron Lett.* **1994**, *35*, 7253.

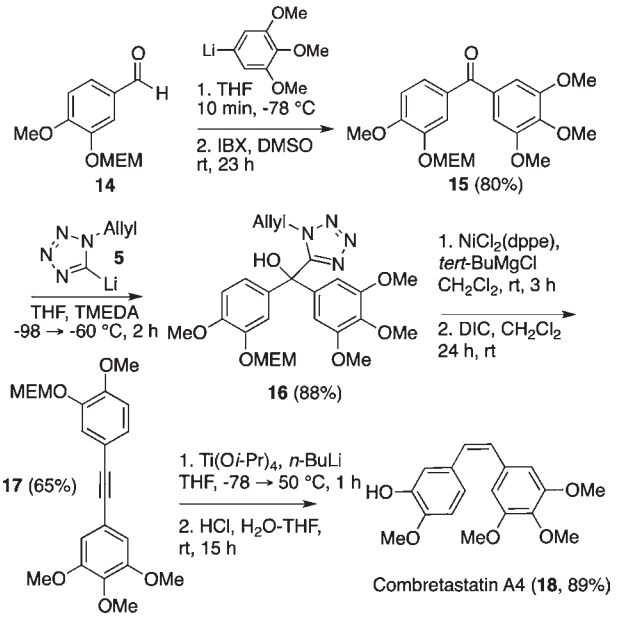
(23) Malatesta, V.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 609–614.

bond in this system relative to the other substrates in which the presence of an adjoining heteroatom favors C−H insertion.[23] Unexpectedly, the formation of 4-azaspiro-[2.4]heptane **13f** was accompanied by a significant amount of [1,2]-rearrangement.

Having established the viability of our methodology in [1,5]-C−H insertions, we turned our attention to its application to natural product synthesis. The dried stem wood of the South African bush willow tree *Combretum caffrum* harbors several biologically active stilbenoid phenols now commonly known as combretastatins. First isolated by Pettit in 1989,[24] combretastatin A4 (**18**) competitively binds the colchicine site of tubulin and is an exceptionally potent inhibitor of microtubule assembly and cellular mitosis. Its selectivity for proliferating endothelial cells and suppression of tumor angiogenesis places **18** and its numerous synthetic analogs[25] in an emerging class of anticancer drugs referred to as vascular disrupting agents.[26]

Our route to combretastatin A4 (**18**) commenced from isovanillin derivative **14**,[27] which underwent addition of 3,4,5-trimethoxyphenyllithium[28] to generate the corresponding benzhydryl alcohol in excellent yield (93%) (Scheme 2). Treatment of this compound with 2-iodoxybenzoic acid (IBX) in DMSO then provided ketone **15**. After tetrazole addition and de-*N*-allylation, treatment of **16** with DIC led to the formation of **17** in good overall yield. Low temperature treatment of this alkyne with $Bu_2Ti(O\textit{i}\text{-}Pr)_2$, generated in situ by treatment of $Ti(O\textit{i}\text{-}Pr)_4$ with *n*-BuLi (2 equiv), and protolytic workup, exclusively provided the *Z*-stilbene.[29] Diastereoselectivity in this case arises through stereospecific diprotonation of the three-membered titanacyle formed by epimetalation of alkyne **17**.[30] Finally, acid hydrolysis of the MEM ether afforded combretastatin A4 (**18**) with an overall yield of 38% from isovanillin. Spectral data collected for synthetic **18** were found to be in complete agreement with those reported by Pettit for the natural product.[31]

Scheme 2



In summary, we have developed a new method for the generation of alkylidenecarbenes involving the dehydration and fragmentation of 5-hydroxyalkyl-1*H*-tetrazoles under exceptionally mild conditions. This methodology displays wide substrate scope and can be utilized for the synthesis of alkynes, diynes, and triynes through the 1,2-rearrangement of the intermediate carbene, or five-membered carbocycles and heterocycles via [1,5]-C−H bond insertion. This chemistry was also successfully utilized in a highly stereoselective total synthesis of combretastatin A4 (**18**), which was accomplished in eight steps from isovanillin with an overall yield of 38%.

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

The authors declare no competing financial interest.

(24) Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendal, D. *Cell. Mol. Life Sci.* **1989**, *45*, 209.

(25) For reviews, see: (a) Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Busacca, S.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 3033. (b) Singh, R.; Kaur, H. *Synthesis* **2009**, 2471.

(26) For reviews, see: (a) Daenen, L. G.; Roodhart, J. M.; Shaked, Y.; Voest, E. E. *Curr. Clin. Pharmacol.* **2010**, *3*, 178. (b) Lippert, J. W., III. *Bioorg. Med. Chem.* **2007**, *15*, 605. (c) Tozer, G. M.; Kanthou, C.; Baguley, B. C. *Nat. Rev. Cancer* **2005**, *5*, 423.

(27) Crombie, L.; Jamieson, S. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1467.

(28) Generation by metalation of 3,4,5-trimethoxyiodobenzene with *tert*-BuLi: Hoye, T. R.; Kaese, P. A. *Synth. Commun.* **1982**, *12*, 49.

(29) While this work was in progress, related approaches to **18** were reported: (a) Lara-Ochoa, F.; Espinosa-Pérez, G. *Tetrahedron Lett.* **2007**, *48*, 7007. (b) Petrov, O. I.; Gerova, M. S.; Chanev, C. D.; Petrova, K. V. *Synthesis* **2011**, 3711.

(30) Eisch, J. J.; Gitua, J. N. *Organometallics* **2003**, *22*, 24.

(31) Pettit, G. R.; Singh, S. B.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Schmidt, J. M.; Hogan, F. *J. Med. Chem.* **1995**, *38*, 1666.