J|A|C|S
COMMUNICATIONS

Published on Web 07/10/2002

Reaction of α,α-Dibromo Oxime Ethers with Grignard Reagents: Alkylative Annulation Providing a Pyrimidine Core

Hirotada Kakiya, Kazunari Yagi, Hiroshi Shinokubo,* and Koichiro Oshima*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501, Japan

Received May 16, 2002

Pyrimidines are an important class of heteroaromatic compounds and have widespread applications from pharmaceuticals to materials.[1] A number of pyrimidines are known to have antimicrobial and antitumor activities, and some of them are presently in use. The electron-deficient nature of pyrimidines can provide highly electron-accepting ability to conjugated polymers.[2] In addition, conjugated molecules which have a pyrimidine core as the key unit have received much attention recently, and they are prospective candidates for light-emitting devices.[3] Pyrimidine also has interesting characteristics as a ligand for a variety of transition metals to construct supramolecules.[4]

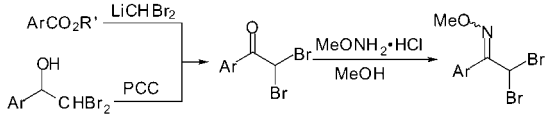
Due to these unique properties, development of synthetic methods which enable rapid access to pyrimidines is desirable. In most cases, synthesis of pyrimidine is based on classical condensation reactions between C−C−C and N−C−N components[5] or cross-coupling reactions.[6] Herein we wish to report a novel construction of a pyrimidine core with incorporation of various alkyl and aryl groups from the corresponding Grignard reagents. The reaction of α,α-dibromo oxime ethers with a variety of Grignard reagents efficiently provides 2,4,6-trisubstituted pyrimidines.

α,α-Dibromo oxime ethers are easily prepared from the corresponding α,α-dibromo ketones upon treatment with *O*-methyl hydroxylamine hydrochloride in methanol. α,α-Dibromo ketones are readily available from the reaction of esters with dibromomethyllithium via Kowalski's protocol[7] or oxidation of dibromomethyl carbinols with PCC (Scheme 1).[8]

To a THF solution of α,α-dibromoacetophenone *O*-methyloxime (**1a**, *Z*/*E* = 84/16) was added 1.1 equiv of butylmagnesium bromide in THF dropwise at 0 °C, and the color of the reaction mixture turned deep purple. The mixture was stirred for 1 h. Aqueous workup and purification afforded 2-butyl-4,6-diphenylpyrimidine (**2a**) in 25% yield (Scheme 2). It then proved to be necessary to employ more than 2.0 equiv of the Grignard reagent to improve the yield. After optimization, treatment of **1a** with 2.2 equiv of *n*-BuMgBr at −42 °C and warming up the reaction mixture to room temperature furnished **2a** in 74% yield.

We examined various Grignard reagents to be incorporated in the pyrimidine core. Not only alkyl groups but also aryl and vinyl groups can be introduced. Table 1 summarizes the results. Several characteristics of this reaction are noteworthy. *p*-Bromophenyl derivative **1e** provides the corresponding pyrimidine **2k** without reduction of bromide. Bromide **2k** is a useful compound for the synthesis of highly conjugated molecules via a Sonogashira-coupling reaction (Scheme 3). Using *p*-bromophenylmagnesium bromide, *p*-bromophenyl group can be introduced at the 2-position of the pyrimidine core providing **2g**. This protocol also enables the synthesis of a heteroaromatic-substituted pyrimidine. Difurylpyrimidine **2l** can be prepared from **1f**.

Scheme 1



Scheme 2

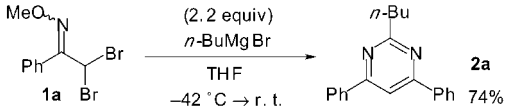
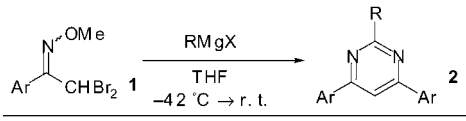
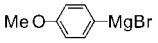
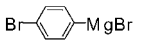
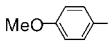
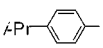
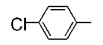
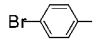


Table 1. Synthesis of Pyrimidines from Dibromo Oxime Ethers[a]



Ar		RMgX		Yield (%)
Ph (**1a**)		*n*-PrMgBr	**2b**	64
Ph (**1a**)		*c*-C_6H_{11}MgBr	**2c**	55
Ph (**1a**)			**2d**	62
Ph (**1a**)		PhMgBr	**2e**	64
Ph (**1a**)			**2f**	75
Ph (**1a**)			**2g**	80
	**1b**	*n*-BuMgBr	**2h**	70
	**1c**	*n*-BuMgBr	**2i**	65
	**1d**	*n*-BuMgBr	**2j**	72
	**1e**	*n*-BuMgBr	**2k**	75
	**1f**	*n*-BuMgBr	**2l**	65

[a] Reaction conditions: Substrates (1.0 mmol), Grignard reagent (2.2 equiv), THF (5 mL), −42 °C then warming the reaction mixture up to room temperature.

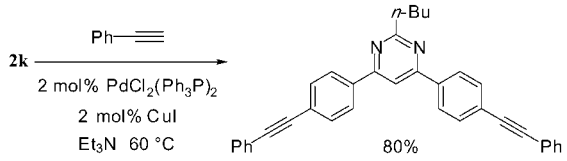
Interestingly, the use of allylic magnesium compounds instead of alkyl or aryl Grignard reagents provided none of the corresponding pyrimidines. Instead, the reaction afforded diallylated aziridines **3a** or **3b** in good yields (Scheme 4).

To obtain mechanistic insights, we carried out the reaction at −98 °C (Scheme 5). Quenching the reaction at −98 °C provided α-bromo oxime ether **4a** exclusively. This result indicates that bromine−magnesium exchange to furnish carbenoid **5** is the initial

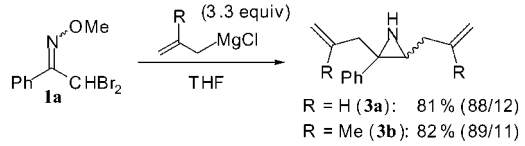
* To whom correspondence should be addressed. E-mail: oshima@fm1.kuic.kyoto-u.ac.jp; shino@fm1.kuic.kyoto-u.ac.jp.

10.1021/ja0269284 CCC: $22.00 © 2002 American Chemical Society

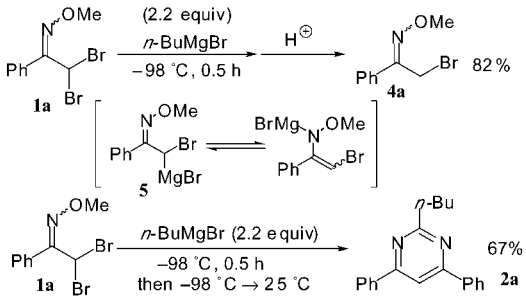
Scheme 3



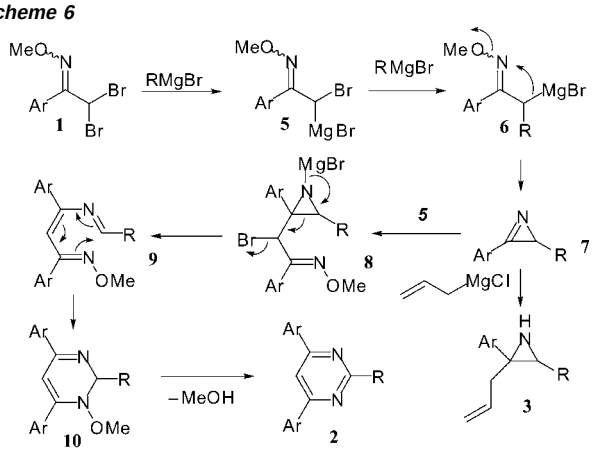
Scheme 4



Scheme 5



Scheme 6



stage.[9] Warming this reaction mixture yielded pyrimidine **2a**. Even at −78 °C, no other intermediary products than **4a** were isolated.

We propose a plausible mechanism involving an azirine intermediate as depicted in Scheme 6. Bromine−magnesium exchange affords carbenoid **5**, which is then alkylated at the α-position with the Grignard reagent to furnish **6**.[10] α-Magnesiated oxime ether **6** undergoes Neber-type cyclization[11] to provide highly reactive azirine **7**.[12] The reaction of azirine with **5** affords **8**, which yields diimine **9** via ring opening. An electrocyclization of **9** provides a pyrimidine skeleton **10**,[13] which is finally converted to pyrimidine **2** upon elimination of methanol. Although the present reaction pathway is speculative, the formation of allylated aziridine **3** from the reaction of **1** with allylmagnesium chloride can support the presence of azirine **7** as the intermediate.[14]

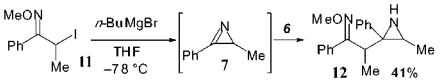
In conclusion, we have achieved a facile synthesis of pyrimidines from α,α-dibromo oxime ethers with a variety of Grignard reagents. The alkyl or aryl group of a Grignard reagent is introduced at the 2-position of the pyrimidine core efficiently.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Area (No. 412: Exploitation of Multi-Element Cyclic Molecules) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. H.K. acknowledges the Research Fellowships of the Japan Society for the Promotion of Science for Young Scientists for financial support.

Supporting Information Available: General procedures, spectral data for compounds, and DFT calculations for electrocyclization of a 1,5-diaza-1,3,5-triene (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Brown, D. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 3, Chapter 2.13.
(2) Gompper, R.; Mair, H.-J.; Polborn, K. *Synthesis* **1997**, 696. Kanbara, T.; Kushida, T.; Saito, N.; Kuwajima, I.; Kubota, K.; Yamamoto, T. *Chem. Lett*. **1992**, 583.
(3) Wong, K.-T.; Hung, T.-S.; Lin, Y.; Wu, C.-C.; Lee, G.-H.; Peng, S.-M.; Chou, C. H.; Su, Y. O. *Org. Lett*. **2002**, *4*, 513.
(4) Hanan, G. S.; Vilkmer, D.; Schubert, U. S.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1842. Bassani, D. M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1845. Semenov, A.; Spatz, J. P.; Möller, M.; Lehn, J.-M.; Sell, B.; Schubert, D.; Weidl, C. H.; Schubert, U. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2547. Harriman, A.; Ziessel, R. Coord. *Chem. Rev*. **1998**, *171*, 331. Harriman, A.; Ziessel, *Chem. Commun*. **1996**, 1707.
(5) Müller, T. J. J. Braum, R.; Ansorge, M. *Org. Lett*. **2000**, *2*, 1967 and references therein.
(6) (a) Schmaker, J. M.; Delia, T. J. *J. Org. Chem*. **2001**, *66*, 7125. (b) Turck, A.; Pré, N.; Lepretre-Gaquere, A.; Queguiner, G. *Heterocycles* **1998**, *49*, 205.
(7) Kowalski, C.; Haque, M. S. *J. Org. Chem*. **1985**, *50*, 5140.
(8) Takahashi, A.; Shibasaki, M. *J. Org. Chem*. **1988**, *53*, 1227, Bacquet, C.; Villieras, J.; Normant, J. F. *Comptes Rendus* **1974**, 929.
(9) (a) Hoffmann, R. W.; Knopff, O.; Kusche, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1462. (b) Hoffmann, R. W.; Hölzer, B.; Knopff, O.; Harms, K. *Angew. Chem., Int. Ed*. **2000**, *39*, 3072.
(10) For reviews on halogen−magnesium exchange, see: (a) Rottländer, M.; Boymond, L.; Bérillon, L.; Leprêtre, A.; Varchi, G.; Avolio, S.; Laaziri, H.; Quéguiner, G.; Ricci, A.; Cahiez, G.; Knochel, P. *Chem. Eur. J*. **2000**, *6*, 767. (b) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.
(11) Recent examples, see: (a) Verstappen, M. M. H.; Ariaans, G. J. A.; Zwanenburg, B. *J. Am. Chem. Soc*. **1996**, *118*, 8491. (b) Palacios, F.; de Retana, A. M. O.; Gil, J. I. *Tetrahedron Lett*. **2000**, *41*, 5363.
(12) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 7, Chapter 5.04.
(13) An electrocyclization of 1,5-diazahexa-1,3,5-trienes has not been well-documented. However, DFT calculations at the B3LYP/6-31G* level show that this process is feasible (E_a = 10.1 kcal/mol). See Supporting Information.
(14) The reaction of **11** with *n*-BuMgBr provided aziridine **12**, which clearly indicates the presence of the azirine intermediate **7** via **6**. We thank a reviewer for suggesting this experiment.



JA0269284