Synthesis of Pyrimidines via Base-induced Condensation of α-Chloro Oxime Derivatives

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A facile synthesis of 2,4,6-trisubstituted pyrimidines from the reaction of α-chloro oxime ethers with Grignard reagents has been developed. Alkyl and aryl groups can be easily introduced at the 2-position of the pyrimidine core. In addition, a synthesis of unsymmetrical pyrimidines has been examined.

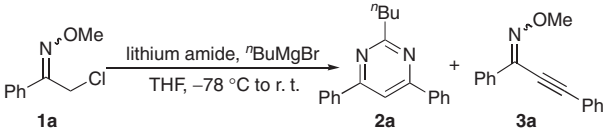
The pyrimidyl heterocyclic core is a common subunit in numerous natural products.[1] Classical condensation reactions of 1,3-dicarbonyl compounds with amidines or amidinium salts can provide substituted pyrimidines. However, there have been relatively few methods available to produce trisubstituted pyrimidines.[2] Recently, we have disclosed that treatment of α,α-dibromo oxime ethers with Grignard reagents provides 2,4,6-trisubstituted pyrimidines.[3] Although the whole reaction mechanism has not yet been clearly elucidated, it is clear that bromine–magnesium exchange takes place to generate a magnesium carbenoid in the initial stage. We anticipated that deprotonation at the α-position of α-halo oxime ethers would also provide the same type of carbenoid, and we set out to develop a pyrimidine synthesis starting from α-halo oxime ethers. From a synthetic point of view, widely available α-halo oxime ethers are undoubtedly superior substrates to α,α-dibromo oxime ethers. Herein we wish to report a base-induced construction of 2,4,6-trisubstituted pyrimidines from α-chloro oxime ethers. Moreover, modification of this method allows for the synthesis of unsymmetrical pyrimidines.

To a THF solution of α-chloroacetophenone *O*-methyloxime (**1a**) was added 1.2 equiv. of lithium diisopropylamide (LDA) in THF dropwise at −78 °C and the mixture was stirred for 15 min. To the resulting mixture was added 1.5 equiv. of butylmagnesium bromide in THF at −78 °C, and gradual warming to room temperature furnished 2-butyl-4,6-diphenylpyrimidine (**2a**) in 38% yield along with 1,3-diphenylpropyn-1-one *O*-methyloxime (**3a**) in 2% yield. After optimization of the reaction conditions, we found that the addition of the Grignard reagent before **1a** improved yield of **2a**. The results obtained in this manner are listed in Table 1. To attain a good conversion, more than 2.0 equiv. of lithium amide is necessary. Interestingly, the bulkiness of lithium amide is crucial. The use of more sterically hindered lithium amides affords higher selectivity (Runs 1–3).

We then investigated the scope and limitations of this procedure. Table 2 summarizes the results. Alkyl, aryl, and vinyl groups can be introduced through the corresponding Grignard reagent.[4] Alkyl substituted α-chloro oxime ethers with α-protons on both sides afforded the pyrimidines in moderate yields (Runs 10–12).

On the basis of these results, we propose a plausible mechanism, which has been modified from our previous proposal (Scheme 1).[3] Deprotonation of α-chloro oxime ether **1** generates carbenoid **4**, which then undergoes Neber-type cyclization[5,6] to provide highly reactive azirine **5**.[7] Nucleophilic addition of **4** to azirine **5** and subsequent intramolecular cyclization yields 2-chloro-1-azabicyclo[1.1.0]butane **7**,[8] which has been postulated as a common intermediate for both pyrimidines and alkynyl oxime ethers. Halide displacement by the alkyl group at the C2 position triggers ring opening to release strain giving imino oxime ether **8**. After an electrocyclization, **9** is converted to pyr-

Table 1. Reaction of carbenoid derived from **1a** with butylmagnesium bromide

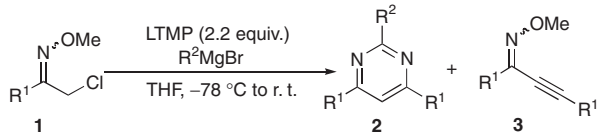


1a 2a 3a

Run	Lithium Amide	/equiv.	^{n}BuMgBr /equiv.	Yield /% 2a	3a
1	LDA	2.0	1.0	63	8
2	$LiNEt_2$	2.2	1.0	34	38
3	LTMP	2.2	1.0	84	4
4	LTMP	2.0	0.5	42	56
5	LTMP	2.0	2.0	71	<1
6[a]	LTMP	1.5	0.5	46	3

[a] **1a** was recovered in 25%.

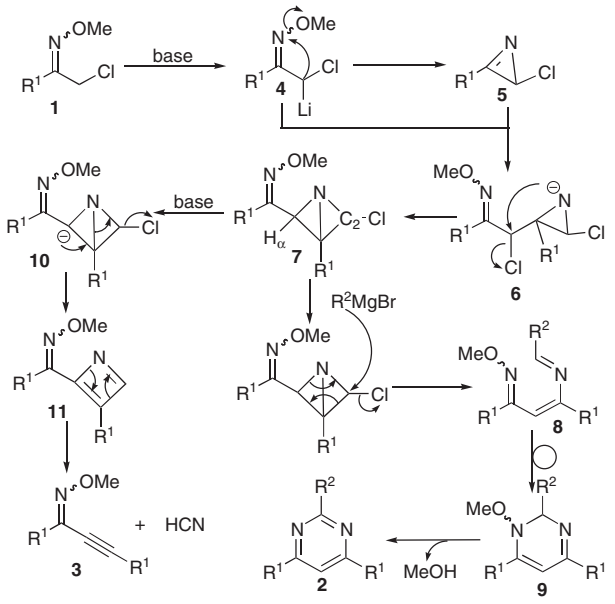
Table 2. Synthesis of pyrimidines



1 2 3

Run	R^1	R^2 /equiv.		Yield /% 2	3
1	Ph **1a**	^{n}Bu	1.0	**2a** 84	**3a** 4
2	**1a**	3-Octenyl	1.1	**2b** 79	**3a** 3
3	**1a**	^{c}Hexyl	1.2	**2c** 76	**3a** 6
4	**1a**	Me[a]	1.1	**2d** 64	**3a** 13
5	**1a**	Ph	2.0	**2e** 63	**3a** 9
6	**1a**	vinyl	2.0	**2f** 64	-
7	4-ClC_6H_4 **1b**	^{n}Bu	1.5	**2g** 83	**3b** <1
8	4-BrC_6H_4 **1c**	^{n}Bu	1.1	**2h** 75	**3c** 8
9	4-$MeOC_6H_4$ **1d**	^{n}Bu	1.0	**2i** 65	**3d** 12
10	^{c}Pen **1e**	^{n}Bu	1.0	**2j** 56	-[b]
11	$^nC_8H_{17}$ **1f**	^{n}Bu	1.2	**2k** 42	-[b]
12[c]	Me **1g**	^{n}Bu	1.2	**2l** 22	-[b]

[a] Methylmagnesium iodide was used. [b] The generation of alkynyl oxime ether was elusive due to the presence of other unidentified products. [c] To a THF solution of **1g** was added LTMP and then added Grignard reagent.



Scheme 1.

imidine **2** upon elimination of methanol.[3] On the other hand, removal of an α-proton of **7** leads to alkynyl oxime ether **3** via cycloreversion of highly unstable azacyclobutadiene intermediate **11**.[9,10] Although the present reaction pathway is still speculative, it is in good agreement with the fact that a sterically hindered lithium amide prefers the generation of pyrimidines to alkynyl oxime ethers.

In our recent study, we developed a cross-condensation reaction to provide alkynyl oxime ether **14** (Eq 1). In this reaction, selective generation of haloazirine from one of two different oxime derivatives is a key issue.[9] The difficulty was circumvented by using a combination of oxime methyl ether **1** and oxime *p*-toluenesulfonate **12** or ethoxycarbonate **13**, where cyclization of carbenoid derived from **12** or **13** proceeded much faster than that of **1**. We tested this methodology to see if it was also applicable for the synthesis of unsymmetrical pyrimidines **15**. After optimization of the reaction conditions, a variety of unsymmetrical pyrimidines **15** were obtained. Several comments are worth noting. 1) Aryl substituted oxime methyl ethers undergo dimerization to provide **2** even at -88 °C (Run 5). At -98 °C the dimerization of **1** is suppressed. On the other hand, carbenoids derived from alkyl substituted oxime methyl ethers are stable at -78 °C under the reaction conditions. 2) The use of an excess of aryl substituted oxime methyl ethers (2.0 equiv.) improved the yield of **15** (Runs 2 and 3). However, this was not the case for alkyl substituted oxime methyl ethers (Runs 9 and 10).

(1)

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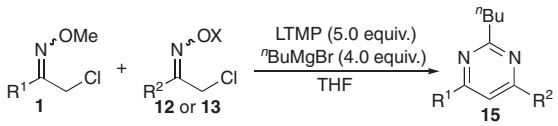
Table 3. Synthesis of unsymmetrical pyrimidines



12a: X = Ts, R^2 = Ph **12b**: X = Ts, R^2 = 4-ClC_6H_4
13a: X = C(O)OEt, R^2 = Ph **13b**: X = C(O)OEt, R^2 = 4-ClC_6H_4

Run	R^1	R^2	T /°C	Yield / %	
				15	**2**
1[a]	4-ClC_6H_4 **1b**	**13a**	−78	**15a** 11	**2g** 68
2[a]	**1b**	**13a**	−98	**15a** 34	
3[b]	**1b**	**13a**	−98	**15a** 56	
4[b]	Ph **1a**	**13b**	−98	**15a** 34	
5[b]	**1a**	**13b**	−88	**15a** 57	**2a** 14
6[c]	4-BrC_6H_4 **1c**	**12a**	−98	**15b** 44	
7[c]	**1c**	**12b**	−98	**15c** 44	
8[a]	^{n}C$_8$H$_{17}$ **1f**	**13a**	−78	**15d** 52	
9[a]	**1f**	**13b**	−78	**15e** 56	
10[b]	**1f**	**13b**	−78	**15e** 23	
11[a]	^{t}BuCH$_2$ **1h**	**13a**	−78	**15f** 60	

[a] The reaction employed **13** (1.1 equiv.), and the yield is based on **1**. [b] The reaction employed **1** (2.0 equiv.), and the yield is based on **13**. [c] The reaction employed **1** (1.6 equiv.), and the yield is based on **12**.

References and Notes

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3 H. Kakiya, K. Yagi, H. Shinokubo, and K. Oshima, *J. Am. Chem. Soc.*, **124**, 9032 (2002).
4 To a solution of LTMP (2.2 mmol) in THF (4 mL) was added a solution of *n*-BuMgBr (1.0 mL, 1.0 M solution in THF, 1.0 mmol) dropwise at -78 °C. To the resulting mixture was added **1a** (183.6 mg, 1.0 mmol) in THF (2 mL) at -78 °C, and the mixture was warmed up to room temperature gradually. After aqueous workup, purification by chromatography afforded **2a** (121.1 mg, 0.42 mmol). Spectral data for **2a** were identical with those reported in the literature.
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10 The generation of HCN was confirmed. see Ref. 9.

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