Hypervalent Iodine in Synthesis 93. A Facile Synthesis of 2-Substituted Imidazo[1,2-*a*]pyrimidines by Cyclocondensation of Alkynyl(phenyl)iodonium Salts and 2-Aminopyrimidine

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Simple stirring of a mixture of the alkynyl(phenyl)iodonium salts **1** with 2- aminopyrimidine **2** in chloroform under reflux for two hours in the presence of K_2CO_3 gave, after workup, the 2-substituted imidazo[1,2-*a*]pyrimidines **3** in moderate to good yields. A possible mechanism for the formation of **3** involves the intramolecular cyclization of the intermediate alkylidenecarbene **6**.

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Introduction.

Imidazo[1,2-*a*]pyrimidines show much importance in pharmaceutical and biochemical fields and some of their derivatives, particularly the 2-substituted derivatives, possess effective antifungal and antibacterial activities [1-3]. Therefore, their synthesis has become increasingly important. To date, various methods for the synthesis of 2-substituted imidazo[1,2-*a*]pyrimidines have been reported [4-18]. Among these procedures, the most conveniently and frequently used was one carried out by cyclocondensation of 2-aminopyrimidine with the appropriate α-halogenoketone (Tschitschibabin method). A variety of starting compounds are available, either commercially or synthetically, for this procedure and it does not require severe reaction conditions. However, this method has the major disadvantage of using lachrymatory and toxic α-halogenoketones.

Alkynyl(phenyl)iodonium salts have found broad application in synthetic organic chemistry [19-23]. Our recent investigations dealing with hypervalent iodine mediated synthesis have shown that the alkynyl(phenyl)iodonium salt is an extremely important equivalent reagent of α-haloketones, providing novel and useful synthesis of various heterocyclic compounds such as 2-mercaptothiazoles [24], selenazoles [25], imidazoles [26] and 2-substituted-imidazo[1,2-*a*]pyridines [27]. As part of our program directed towards the use of hypervalent iodine reagents in organic synthesis, we were interested in the development of a new synthetic method using alkynyl(phenyl)iodonium salts to replace α-haloketones for the synthesis of five-membered heterocyclic compounds. We tried to examine the reaction of alkynyl(phenyl)iodonium salts with 2-aminopyrimidine for providing a new route to 2-substituted imidazo[1,2-*a*]pyrimidines. Herein, we would like to report our results, a new facile synthesis of 2-substituted imidazo[1,2-*a*]pyrimidines by cyclocondensation of alkynyl(phenyl)iodonium salts with 2-aminopyrimidine.

Results and Discussion.

We found that the cyclocondensation of alkynyl-(phenyl)iodonium salts with 2-aminopyrimidine occurred easily in $CHCl_3$ in the presence of K_2CO_3. In fact, simple stirring of a mixture of the alkynyl(phenyl)iodonium salts **1** with 2-aminopyrimidine **2** in chloroform under gentle reflux for two hours in the presence of K_2CO_3 gave, after workup, the corresponding 2-substituted imidazo[1,2-*a*]pyrimidines **3** in moderate to good yields (Scheme 1). The results are summarized in Table 1.

Scheme 1

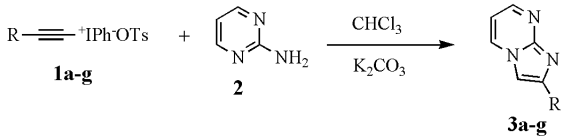


Table 1

Preparation of 2-Substituted-imidazo[1,2-*a*]pyrimidines **3a-g**

3	R	Yield (%) [a]
a	C_6H_5	69
b	4-F-C_6H_4	78
c	4-Cl-C_6H_4	80
d	4-Br-C_6H_4	75
e	$MeOCH_2$	57
f	$EtOCH_2$	61
g	4-MeO-C_6H_4	66

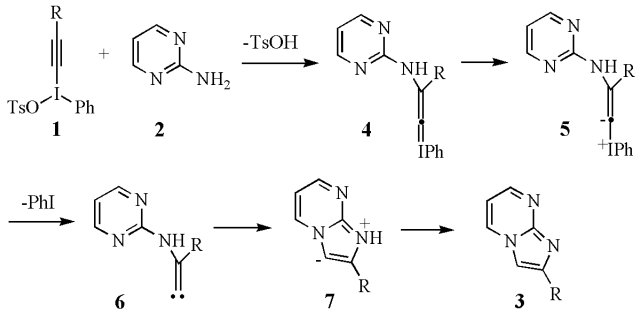
[a] Isolated yield based on alkynyl(phenyl)- iodonium salt **1**.

The reaction was found to be general and applicable to alkylethynyl(phenyl)iodonium salts and arylethynyl(phenyl)-iodonium salts. Several arylethynyl(phenyl)iodonium salts containing various substituents, such as fluoro, chloro, bromo and methoxy groups were successfully reacted.

In order to examine the regiochemistry of the reaction, we then performed the reaction by cyclocondensation of α-bromo-*p*-fluoroacetophenone with 2- aminopyrimidine according to standard procedure [5]. The product obtained by this method is known to be 2-(*p*-fluorophenyl)imidazo[1,2-*a*]pyrimidine, which is identical in respects with the product prepared by our present method. Therefore, **3** is proved to be 2-substituted imidazo[1,2-*a*]-pyrimidines, not the 3-substituted isomers. All products were also characterized by mp, IR spectral data and microanalyses. They are identical to the data reported by the literature. The spectral data are summarized in the experimental section.

A possible mechanism for the formation of 2-substituted imidazo[1,2-*a*]pyrimidines **3** may involve the electrophilic attack of the β-carbon of alkynyl(phenyl)iodonium salts **1** on the exocyclic nitrogen to form the primary addition products **4**, followed by 1,1-elimination of iodobenzene to generate the carbene **6**, and cycloaromatization of **6** to give 2-substituted imidazo[1,2-*a*]pyrimidines **3** (Scheme 2).

Scheme 2



Conclusion

The present study provides a new facile method of synthesis of 2-substituted imidazo[1,2-*a*]pyrimidines by cyclocondensation of alkynyl(phenyl)iodonium salts with 2-aminopyrimidine, which has some advantages over existing methods such as avoiding the use of lachrymatory and toxic α-halogenoketones, mild reaction conditions, ready availability of starting materials and short reaction time. Furthermore, the range of useful applications of alkynyl(phenyl)iodonium salts in organic chemistry has been extended.

EXPERIMENTAL

Melting points were determined on a X_4- Data microscopic melting point apparatus and were uncorrected. Microanalyses were obtained using Carlo-Erba 1106. ^{1}H NMR spectra were obtained at 400 MHz in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 683 spectrometer at room temperature.

General Procedure for the Preparation of 2-Substituted imdazo[1,2-*a*]pyrimidines **3a-g**.

To a solution of 2-aminopyrimidine (1.2 mmol) in $CHCl_3$ (15 mL) was added K_2CO_3 (0.6 mmol). While stirring, the corresponding alkynyl(phenyl)iodonium salt (1 mmol) was added to the mixture. The resulting mixture was refluxed for 2 hours and water (20 mL) was added. The chloroform phase was dried (Na_2SO_4), concentrated and chromatographed on a silical gel plate using petroleum ether (b.p. 60-90°)/Et_2O (4:1) as eluent to afford the 2-substituted imdazo[1,2-*a*]pyrimidine.

2-Phenylimidazo[1,2-*a*]pyrimidine (**3a**) [5].

This compound was obtained as a white powder, mp 196-197°; lit. mp 202°; ir (potassium bromide): 3080, 1680, 830 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.06 (dd, 1H, J_1 = 6.7 Hz, J_2 = 4.1 Hz), 7.36 (t, 1H, J = 7.4 Hz), 7.47 (t, 2H, J = 7.4 Hz), 8.00 (d, 2H, J = 7.1 Hz), 8.38 (s, 1H), 8.53 (dd, 1H, J_2 = 4.1 Hz, J_3 = 2.0 Hz), 8.96 (dd, 1H, J_1 = 6.7 Hz, J_3 = 2.0 Hz).

2-(*p*-Fluorophenyl)imidazo[1,2-*a*]pyrimidine (**3b**) (This Procedure).

This compound was obtained as a white powder, mp 237°; lit. mp 238°; ir (potassium bromide): 3085, 1685, 1220 (C-F), 830 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 6.88 (dd, 1H, J_1 = 6.8 Hz, J_2 = 4.0 Hz), 7.15 (t, 2H, J = 8.8 Hz), 7.79 (s, 1H), 8.02 (dd, 2H, J_1 = 8.8 Hz, J_2 = 5.6 Hz), 8.44 (dd, 1H, J_1 = 6.8 Hz, J_3 = 2.0 Hz), 8.55 (dd, 1H, J_2 = 4.0 Hz, J_3 = 2.0 Hz).

2-(*p*-Fluorophenyl)imidazo[1,2-*a*]pyrimidine (Standard Procedure) [5].

This compound was obtained as a white powder, mp 236-237°; lit. mp 238°; ^{1}H nmr ($CDCl_3$): δ 6.88 (dd, 1H, J_1 = 6.8 Hz, J_2 = 4.0 Hz), 7.15 (t, 2H, J = 8.4 Hz), 7.79 (s, 1H), 8.02 (dd, 2H, J_1 = 8.4 Hz, J_2 = 5.6 Hz), 8.44 (dd, 1H, J_1 = 6.8 Hz, J_3 = 2.0 Hz), 8.55 (dd, 1H, J_2 = 4.0 Hz, J_3 = 2.0 Hz).

2-(*p*-Chlorophenyl)imidazo[1,2-*a*]pyrimidine (**3c**) [5].

This compound was obtained as a white powder, mp 271°; lit. mp 274°; ir (potassium bromide): 3083, 1685, 825 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.05 (dd, 1H, J_1 = 4.0 Hz, J_2 = 6.8 Hz), 7.52 (d, 2H, J = 8.8 Hz), 8.01 (d, 2H, J = 8.8 Hz), 8.40 (s, 1H), 8.53 (dd, 1H, J_1 = 4.0 Hz, J_3 = 1.6 Hz), 8.96 (dd, 1H, J_2 = 6.8 Hz, J_3 = 1.6 Hz).

2-(*p*-Bromophenyl)imidazo[1,2-*a*]pyrimidine (**3d**) [17,18].

This compound was obtained as a white powder, mp 224°; lit. mp 226°; ir (potassium bromide): 3080, 1680, 825 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 7.05 (dd, 1H, J_1 = 4.0 Hz, J_2 = 6.8 Hz), 7.65 (d, 2H, J = 8.4 Hz), 7.94 (d, 2H, J = 8.4 Hz), 8.40 (s, 1H), 8.52 (dd, 1H, J_1 = 4.0 Hz, J_3 = 1.6 Hz), 8.95 (dd, 1H, J_2 = 6.8 Hz, J_3 = 1.6 Hz).

2-Methoxymethylimidazo[1,2-*a*]pyrimidine (**3e**).

This compound was obtained as a white powder, mp 63-65°; ir (potassium bromide): 3060, 1672, 825 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.50 (s, 3H), 4.72 (s, 2H), 6.86 (dd, 1H, J_1 = 4.4 Hz, J_2 = 6.8 Hz), 7.54 (s, 1H), 8.42 (dd, 1H, J_1 = 4.4 Hz, J_3 = 2.0 Hz), 8.54 (dd, 1H, J_2 = 6.8 Hz, J_3 = 2.0 Hz).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.86; H, 5.53; N, 25.73.

2-Ethoxymethylimidazo[1,2-*a*]pyrimidine (**3f**).

This compound was obtained as a white powder, mp 68-69°; ir (potassium bromide): 3055, 1670, 825 cm^{-1}; ^1H nmr ($CDCl_3$): δ1.24 (t, 3H, J = 4.4 Hz), 3.68 (q , 2H, J = 4.4 Hz), 4.76 (s, 2H), 6.86 (dd, 1H, J_1 = 4.0 Hz, J_2 = 6.4 Hz), 7.54 (s, 1H), 8.40 (dd, 1H, J_2 = 6.4 Hz, J_3 = 1.6 Hz), 8.53 (dd, 1H, J_1 = 4.0 Hz, J_3 = 1.6 Hz).

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.96; H, 6.26; N, 23.66.

2-(*p*-Methoxyphenyl)imidazo[1,2-*a*]pyrimidine (**3g**) [16].

This compound was obtained as a white powder, mp 188°; lit. mp 190°; ir (potassium bromide): 3075, 1660, 820 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.81 (s, 3H), 7.05 (m, 3H), 7.94 (d, 2H, J = 8.8 Hz), 8.28 (s, 1H), 8.50 (dd, 1H, J_2 = 6.4 Hz, J_3 = 1.2 Hz), 8.93 (d, 1H, J_1 = 3.6 Hz, J_3 = 1.2 Hz).

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