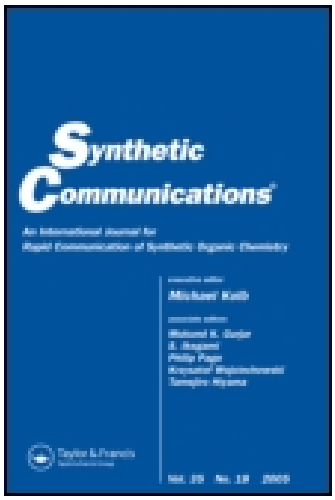

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Hypervalent Iodine in Synthesis. 94. A Facile Synthesis of 2-Substituted-imidazo[1,2-a]pyridines by Cyclocondensation of Alkynyl(phenyl) iodonium Salts and 2-Aminopyridine

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Published online: 18 Oct 2011.

To cite this article: Zhi Liu, Zhen-Chu Chen & Qin-Guo Zheng (2004) Hypervalent Iodine in Synthesis. 94. A Facile Synthesis of 2-Substituted-imidazo[1,2-a]pyridines by Cyclocondensation of Alkynyl(phenyl) iodonium Salts and 2-Aminopyridine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:2, 361-367, DOI: 10.1081/SCC-120027273

To link to this article: http://dx.doi.org/10.1081/SCC-120027273

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 2, pp. 361–367, 2004

Hypervalent Iodine in Synthesis. 94. A Facile Synthesis of 2-Substituted-imidazo[1,2-a]pyridines by Cyclocondensation of Alkynyl(phenyl) iodonium Salts and 2-Aminopyridine

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ABSTRACT

A facile method for the synthesis of 2-substituted-imidazo[1,2-a]pyridines is achieved by cyclocondensation of alkynyl(phenyl)iodonium salts with 2-aminopyridine.

Key Words: Hypervalent iodine; 2-Substituted-imidazo[1,2-a]pyridines; Cyclocondensation; Alkynyl(phenyl)iodonium salts.

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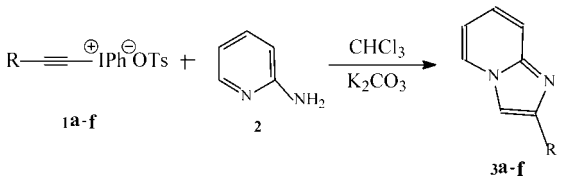
DOI: 10.1081/SCC-120027273 0039-7911 (Print); 1532-2432 (Online)

Our recent investigations dealing with hypervalent iodine mediated synthesis have shown that the phenylethynyl(phenyl)iodonium salt is an extremely important equivalent reagent of the highly lachrymatory α-halogenoacetophenone, providing new and useful synthesis of various heterocyclic compounds such as 2-mercaptothiazoles,[1] selenazoles[2] and 3-substituted-5,6-dihydroimidazo[2,1-b]thiazoles.[3] This new approach has obvious advantages over the literature methods such as simple experimentation and avoiding the use of lachrymatory, toxic and not readily available α-halogeno-ketones. These encouraging results coupled with the ready availability and high reactivity of alkynyl(phenyl)iodonium salts prompted us to examine their reaction with 2-aminopyridine for providing a new and facile synthesis of bridgehead heterocyclic compounds, namely, 2-substituted-imidazo[1,2-a]pyridines. Part of our reason for undertaking this study was that 2-substituted-imidazo[1,2-a]pyridines are known to possess important biological properties such as anti-inflammatory,[4] antifungal,[5] long-acting local anesthetic,[6] antiulcer[7] and anthelmintic or bacterostatic[8] activities. Several derivatives have also been described as fluorescent materials.[9,10] Herein we would like to report a new facile method for the synthesis of 2-substituted-imidazo[1,2-a]pyridines by cyclocondensation of alkynyl(phenyl)iodonium salts with 2-aminopyridine.

We found that the cyclocondensation of alkynyl(phenyl)iodonium salts with 2-aminopyridine occurred easily in $CHCl_3$ under reflux in the presence of K_2CO_3. Thus, simple stirring of a mixture of the alkynyl(phenyl)iodonium salts **1** with 2-aminopyridine **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]pyridines **3** in moderate to good yield (Sch. 1). The results are summarized in Table 1.

The products were characterized by mp, ^{1}H NMR, IR spectral data and microanalyses. They are identical to the data reported by the literature.

The reaction was found to be applicable to arylethynyl(phenyl)iodonium salts possessing various substituents, such as fluoro, chloro, bromo, alkyl and alkoxy groups.



Scheme 1.

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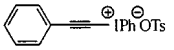
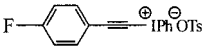
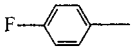
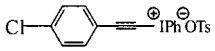
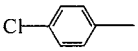
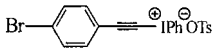
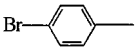
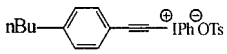
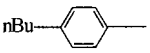
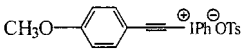
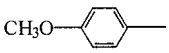
Table 1. Synthesis of 2-substituted-imidazo[1,2-a]pyridines by cyclocondensation of alkynyl(phenyl)iodonium salts and 2-aminopyridine.

Entry	Alkynyl(phenyl)iodonium salts	**3**	Product **3**, R =	Yield (%)[a]
1		**3a**		65
2		**3b**		71
3		**3c**		63
4		**3d**		67
5		**3e**		55
6		**3f**		53

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

A plausible mechanism for the formation of 2-substituted-imidazo[1,2-a]pyridines **3** can be reasoned from the synthesis of thiazoles by cyclocondensation of alkynyl(phenyl)iodonium salts and thioamides[11] and is shown in Sch. 2. It involves the attack of the iodonium ion of alkynyl(phenyl)iodonium salts **1** on the nitrogen of pyridine to form the primary addition products **4** followed by a polyhetero-claisen rearrangement[12] and 1,1-elimination of iodobenzene to generate the carbene **7**, and cycloaromatization of **7** to give 2-substituted-imidazo[1,2-a]pyridines **3**.

Due to the increasing interest in 2-substituted-imidazo[1,2-a]pyridines, there are several methods for their synthesis involving (a) reaction of α-halocarbonyl-compounds with 2-aminopyridine (Tschitschibabin method),[13] (b) reaction of 2-chloropyridine with triazole, and subsequent elimination of nitrogens,[14] (c) intramolecular photocyclization of styrylimidazole,[15] (d) reaction of an α-bromoacyl derivative with sulfonohydrazide and subsequently with pyridine,[16] and (e) pyridine ring formation starting from imidazole compounds.[9] However, these methods often suffer from lengthy sequences, low overall yields, drastic reaction conditions and the use of lachrymatory, toxic or relatively inaccessible starting materials. Our present reaction represents a new facile method for synthesis of 2-substituted-imidazo[1,2-a]pyridines by cyclocondensation of alkynyl(phenyl)iodonium salts and 2-aminopyridine which has some advantages over existing ones such as avoiding the use of lachrymatory and toxic α-halogenoketones, mild reaction conditions, ready availability of starting materials and short reaction

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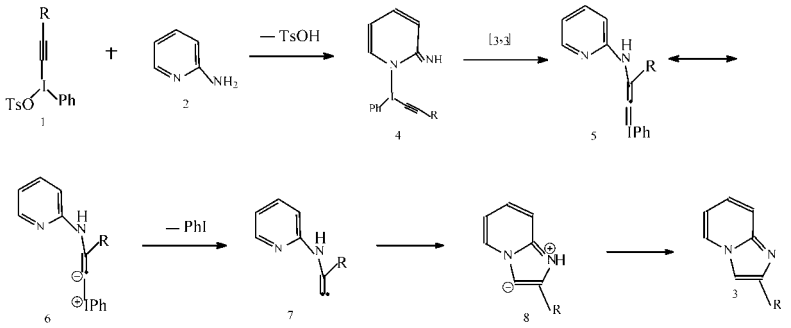

Scheme 2.

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 DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. IR spectra were recorded on a Perkin–Elmer 683 spectrometer at r.t.

General Procedure for the Preparation of 2-Substituted-imidazo[1,2-a]pyridines

To a solution of 2-aminopyridine (1.2 mmol) in $CHCl_3$ (15 mL) was added K_2CO_3 (0.6 mmol). While stirring, the corresponding alkynyl(phenyl)-iodonium salts (1 mmol) was added to the mixture. The resulting mixture was refluxed for 2hrs 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°C)/Et_2O (4 : 1) as eluent to afford the product.

2-Phenyl-imdazo[1,2-a]pyridine, 3a. White powder, m.p.: 133°C (Lit[10] 134°C). IR (KBr): 1634, 830. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.03 (1H, t, $J = 6.8$ Hz), 7.45 (1H, t, $J = 8.4$ Hz), 7.53 (1H, dd, $J_1 = 4.3$ Hz, $J_2 = 8.4$ Hz), 7.60 (4H, d, $J = 4.3$ Hz), 7.79 (1H, s), 7.99 (1H, d, $J = 8.4$ Hz), 8.42 (1H, d, $J = 6.8$ Hz).

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2-(4′-Fluorophenyl)-imdazo[1,2-a]pyridine, 3b. White powder, m.p.: 164-165°C (Lit[10] 169°C). IR (KBr): 1645, 1217, 838. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.21–7.24 (2H, m), 7.31 (1H, t, $J = 6.8$ Hz), 7.72 (1H, t, $J = 8.4$ Hz), 7.92 (1H, s), 8.10 (2H, q), 8.36 (1H, d, $J = 6.8$ Hz), 8.41 (1H, d, $J = 8.4$ Hz).

2-(4′-Chlorophenyl)-imdazo[1,2-a]pyridine, 3c. White powder, m.p.: 205–206°C (Lit[17] 208°C). IR (KBr): 1640, 835, 710. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.80 (1H, t, $J = 6.8$ Hz), 7.22 (1H, t, $J = 8.0$ Hz), 7.40 (2H, d, $J = 8.4$ Hz), 7.65 (1H, d, $J = 8.0$ Hz), 7.83 (1H, s), 7.87 (2H, d, $J = 8.4$ Hz), 8.11 (1H, d, $J = 6.8$ Hz).

2-(4′-Bromophenyl)-imdazo[1,2-a]pyridine, 3d White powder, m.p.: 213–214°C (Lit[10] 215–217°C). IR (KBr): 1638, 830, 506. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.92 (1H, t, $J = 6.8$ Hz), 7.32 (1H, t, $J = 8.0$ Hz), 7.54 (2H, d, $J = 8.0$ Hz), 7.71 (1H, d, $J = 8.0$ Hz), 7.82 (2H, d, $J = 8.0$ Hz), 7.91 (1H, s), 8.18 (1H, d, $J = 6.8$ Hz).

2-(4′-Butylphenyl)-imdazo[1,2-a]pyridine, 3e. White powder, m.p.: 153–155°C. IR (KBr): 2980, 1640, 828. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.94 (3H, t, $J = 7.6$ Hz), 1.39 (2H, m), 1.64 (2H, m), 2.67 (2H, t, $J = 8.0$ Hz), 6.80 (1H, t, $J = 6.8$ Hz), 7.20 (1H, t, $J = 7.2$ Hz), 7.31 (2H, d, $J = 8.0$ Hz), 7.44 (2H, d, $J = 8.0$ Hz), 7.68 (1H, s), 7.70 (1H, d, $J = 6.8$ Hz), 8.31 (1H, d, $J = 7.2$ Hz). Anal. Calcd. for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.48; H, 7.24; N, 11.28.

2-(4′-Methoxyphenyl)-imdazo[1,2-a]pyridine, 3f. White powder, m.p.: 133–135°C (Lit[10] 136°C). IR (KBr): 1635, 1248, 825. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.80 (3H, s), 6.87 (1H, t, $J = 6.8$ Hz), 7.01 (2H, d, $J = 8.0$ Hz), 7.22 (1H, t, $J = 6.8$ Hz), 7.55 (1H, d, $J = 9.6$ Hz), 7.90 (2H, d, $J = 8.0$ Hz), 8.29 (1H, s), 8.50 (1H, d, $J = 6.4$ Hz).

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Received in the UK May 7, 2003

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