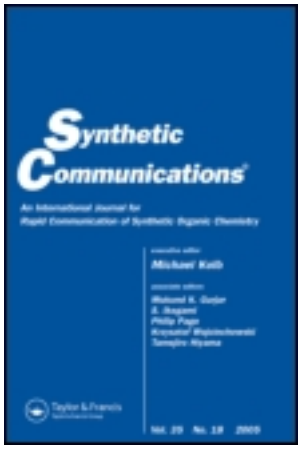


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Synthesis of 3-Substituted 1,2,4-Triazolo[4,3-a]pyridine by [Bis(Trifluroacetoxy)iodo]benzene-Catalyzed Oxidative Intramolecular Cyclization of Heterocyclic Hydrazones

Vikas S. Padalkar [a], Vikas S. Patil [a], Kiran R. Phatangare [a], Prashant G. Umape [a] & N. Sekar [a]
[a] Institute of Chemical Technology, Matunga, Mumbai, India
Published online: 25 Feb 2011.

To cite this article: Vikas S. Padalkar , Vikas S. Patil , Kiran R. Phatangare , Prashant G. Umape & N. Sekar (2011) Efficient Synthesis of 3-Substituted 1,2,4-Triazolo[4,3-a]pyridine by [Bis(Trifluroacetoxy)iodo]benzene-Catalyzed Oxidative Intramolecular Cyclization of Heterocyclic Hydrazones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:6, 925-938

To link to this article: http://dx.doi.org/10.1080/00397911003707162

Synthetic Communications®, 41: 925–938, 2011

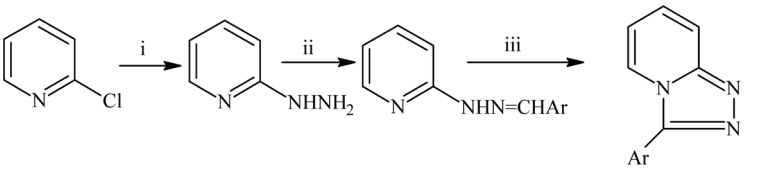
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911003707162

Taylor & Francis
Taylor & Francis Group

EFFICIENT SYNTHESIS OF 3-SUBSTITUTED 1,2,4-TRIAZOLO[4,3-a]PYRIDINE BY [BIS(TRIFLUROACETOXY)IODO]BENZENE-CATALYZED OXIDATIVE INTRAMOLECULAR CYCLIZATION OF HETEROCYCLIC HYDRAZONES

Vikas S. Padalkar, Vikas S. Patil, Kiran R. Phatangare, Prashant G. Umape, and N. Sekar
Institute of Chemical Technology, Matunga, Mumbai, India

GRAPHICAL ABSTRACT



i : $NH_2NH_2.H_2O$ **ii : Susbstituted Aldehyde**

iii: [Bis(trifluroacetoxy)iodo]benzene

Abstract *A series of 1,2,4-triazolopyridines have been prepared by oxidative intramolecular cyclization of heterocyclic hydrazones with [bis(trifluroacetoxy)iodo]benzene. General applicability of this simple transformation was confirmed by synthesis of 1,2,4-triazolo [4,3-a]pyridine. The advantages of this protocol are the nontoxicity of catalyst and shorter reaction time to obtain good preparative yield.*

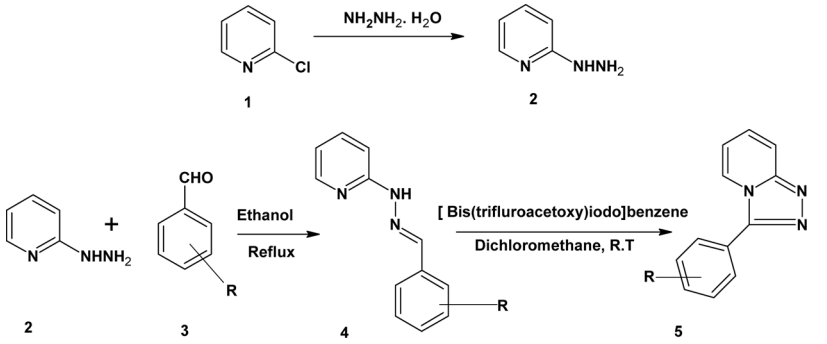
Keywords [Bis(trifluroacetoxy)iodo]benzene; hydrazones; oxidation; 1,2,4-triazole

INTRODUCTION

Triazolopyridines represent an important class of heterocyclic compounds having a wide range of pharmaceutical and biological activities including herbicidal, antifungal, anticonvulsant, and anxiolytic activities.[1] A simple, versatile, and widely applicable method for the synthesis of 1,2,4-triazolopyridine is therefore of considerable interest. The available methods for the preparation of triazolopyridine are based on heterocyclic hydrazones or hydrazides as precursors. However, these methods have some restrictions as regards to their applicability as they involve the use of toxic reagents such as phosphorus oxychloride,[2] lead tetra-acetate,[2,3] bromine,[3,4] and

Received December 8, 2009.

Address correspondence to N. Sekar, Institute of Chemical Technology, Matunga, Mumbai 400 019, India. E-mail: sekarnm@rediffmail.com



Scheme 1. Synthesis of 3-substituted 1,2,4-triazolo[4,3-a]pyridine from 2-chloropyridine.

oxidation of 2-pyridylhydrazones with nitrobenzene at reflux temperature.[5] Recently, synthetic methodologies have been developed using PS-PPh_3/CCl_3 under microwave heating,[6] (diacetoxy) iodo benzene,[7] and oxidant chloroamine T,[8] as well as electrochemical methods.[9] However, they also have some limitations such as moisture sensitivity of the reagents, use of hazardous chemicals, and difficulty in storage of reagents.

As a part of our ongoing research on 1,2,4-triazoles and to overcome the limitations of the reported methods for the synthesis of 1,2,4-triazolopyridine, we describe here in this letter a simple, efficient protocol for the synthesis of 1,2,4-triazolopyridine by oxidative heterocyclization of hydrazones using [bis(trifluroacetoxy) iodo]benzene.

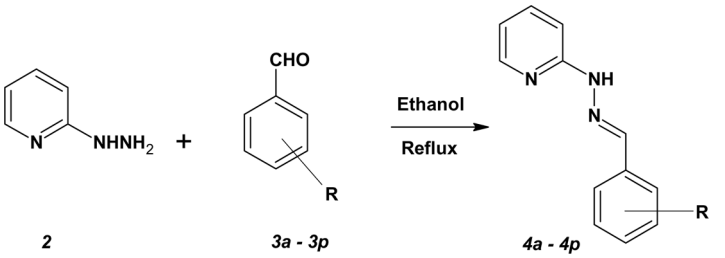
Hypervalant iodine regents have found widespread applications in organic synthesis because of their selectivity and simplicity in use.[10,11] [Bis(trifluroacetoxy)-iodo]benzene is commercially available as a colorless crystalline solid. It is fairly stable and can be kept without refrigeration for a long time with protection from light. It is used for the synthesis of bridgehead heterocycles, synthesis of N-arylated and N-alkylated heterocyclic fused aromatic compounds,[12] synthesis of pyrrolidinone and lactone skeletons,[13] oxidative deprotection of dithiane-containing alkaloids,[14] direct α-hydroxylation of ketones,[15] and synthesis of azides.[16] In this communication, we explore the applicability of [bis(trifluroacetoxy)iodo]benzene (Scheme 1).

RESULTS AND DISCUSSION

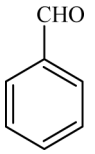
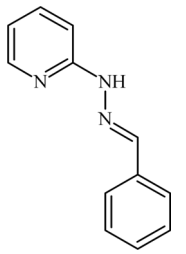
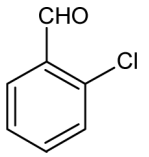
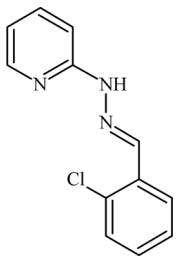
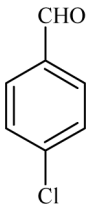
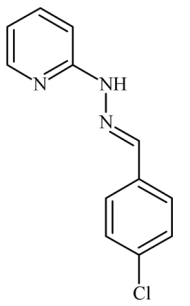
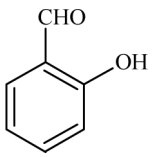
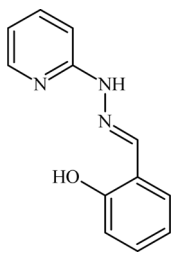
Reaction of 2-chloropyridine **(1)** with hydrazine hydrate at a reflux temperature resulted in the formation of 2-hydrazinopyridine **(2)**. Further condensation with different aldehydes **(3)** in ethanol at a reflux temperature gave the corresponding hydrazones **(4)** with high yield and purity. The hydrazones thus obtained were oxidized by using [bis(trifluroacetoxy)iodo]benzene to give the corresponding 3-substituted 1,2,4-triazolo[4,3-a]pyridine **(5)**.

Initially, the reaction of 2-hydrazinopyridine with benzaldehyde was carried out in ethanol at reflux temperature as model reaction to explore the suitable reaction condition for preparation of different hydrazones (Table 1, entry a).

Table 1. Synthesis of heterocyclic hydrazones from 2-hydrazinopyridine and different substituted aldehydes

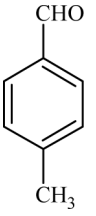
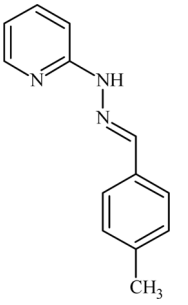
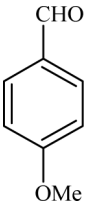
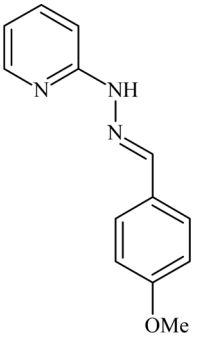
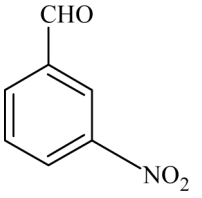
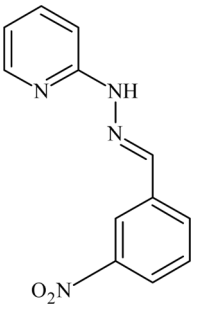
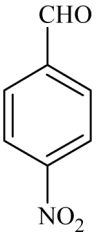
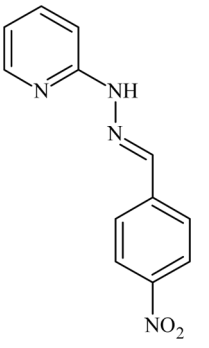


2 *3a - 3p* *4a - 4p*

Entry	Aldehyde **(3)**	Product **(4)**	Yield (%)	Mp (°C)
a			92	148
b			98	189
c			98	195
i			98	215

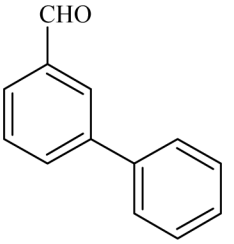
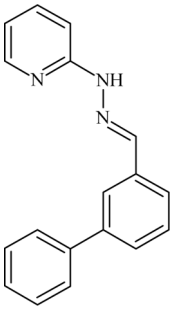
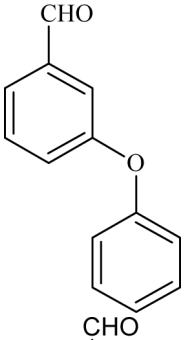
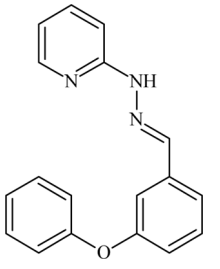
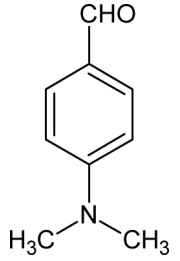
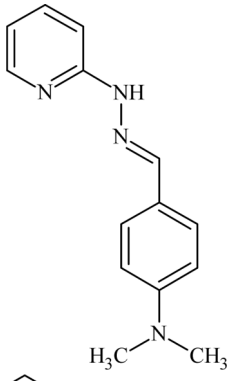
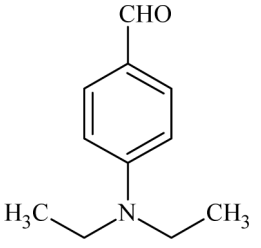
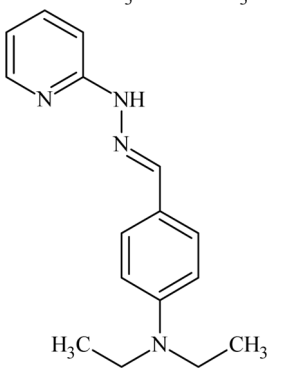
(*Continued*)

Table 1. Continued

Entry	Aldehyde **(3)**	Product **(4)**	Yield (%)	Mp (°C)
e			92	153
f			96	158
g			89	223
h			87	220

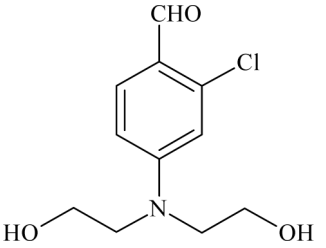
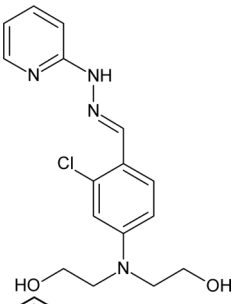
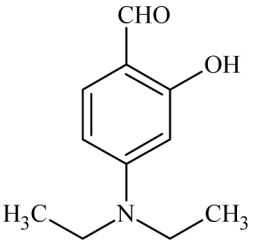
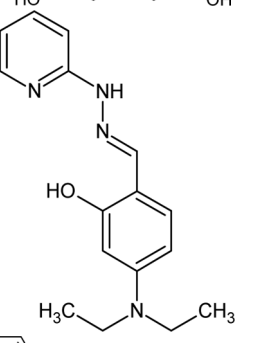
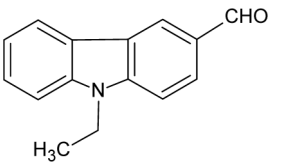
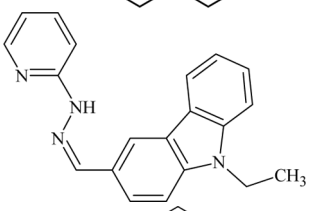
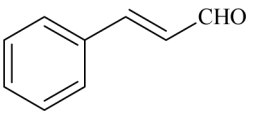
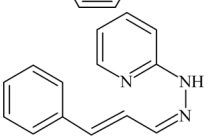
(*Continued*)

Table 1. Continued

Entry	Aldehyde **(3)**	Product **(4)**	Yield (%)	Mp (°C)
i			90	128
j			82	167
k			91	182
l			93	158

(*Continued*)

Table 1. Continued

Entry	Aldehyde **(3)**	Product **(4)**	Yield (%)	Mp (°C)
m			89	189
n			92	175
o			94	185
p			92	164

[a]Reagents and reaction conditions: 2-hydrazinopyridine (10 mmol), aldehydes (10 mmol); solvent: ethanol; temperature: reflux temperature; time: 20 min.
[b]Starting compound 2-hydrazinopyridine prepared by the standard reported procedure.
[c]Isolated yield.
[d]Compounds were confirmed by physical constants.

Subsequently, the reaction was extended with different substituted aldehydes carrying both electron-releasing as well as electron-withdrawing substituents.

Heterocyclization was carried out in dichloromethane at room temperature. To identify an optimal reaction condition for oxidative heterocyclization to the desired triazolopyridine **5**, various solvents were studied (Table 2) at different temperatures with heterocyclization of 2-[(2*E*)-2-benzylidenehydrazinyl] pyridine as the model reaction (Table 3, entry a) in the presence of [bis (trifluroacetoxy) iodo] benzene.

Table 2. Optimization of reaction condition for the synthesis of triazolopyridine

Entry	Solvent	Yield[a]	Temp. (°C)
1	CH_3CN	59	75
2	THF	71	75
3	CH_2Cl_2	94	25
4	CCl_4	75	60
5	MeOH	63	55

[a]Isolated yield after crystallization in benzene.

Note. Catalyst: [bis(trifluroacetoxy)iodo]benzene (11 mmol equivalent); time: 10 min.

Encouragingly, we quickly noticed that when dichloromethane was used as a solvent, compound **5** was obtained with complete conversion as confirmed by thin-layer chromatography (TLC). Subsequently, we were delighted to discover that nearly quantitative conversion to **5** was observed when the reaction is carried out in dichloromethane at room temperature.

These conditions were used further to study the scope of the transformation. Gratifyingly, this paradigm was found to be quite general and worked well for both electron-donating and electron-withdrawing heterocyclic hydrazones to afford the desired triazolopyridine in excellent yields (Table 3) in a short reaction time. The reaction proved to have facile workup.

CONCLUSION

In conclusion, we have developed an efficient and simple protocol for the synthesis of a wide variety of 1,2,4-triazolo compounds by oxidation of heterocyclic substituted hydrazones using trivalent iodine regent [bis(trifluroacetoxy)iodo]benzene at room temperature. The method developed is mild and gives good yield of 1,2,4-triazolo(4,3-a)pyridine starting from 2-chloropyridine. We believe that this approach provides the advantage for both focused library synthesis and diversity-oriented synthesis.

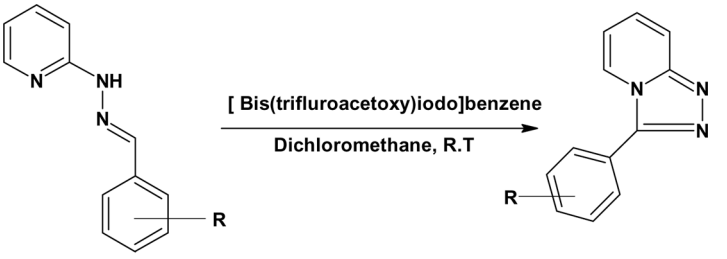
EXPERIMENTAL

All commercial reagents and solvents were procured from S. D. Fine chemicals (India) and were used without further purification. The reaction was monitored by TLC using 0.25-mm E-Merck silica-gel 60 F_{254} precoated plates, which were visualized with ultraviolet light. Melting points were measured on a standard melting-point apparatus from Sunder Industrial Product Mumbai and are uncorrected. ^{1}H NMR spectra were recorded on VXR 400-MHz instrument using tetramethylsilane (TMS) as an internal standard.

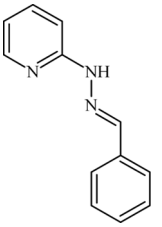
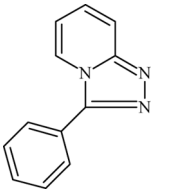
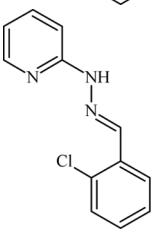
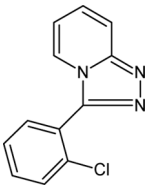
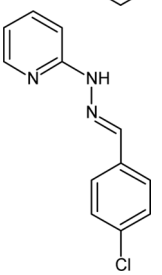
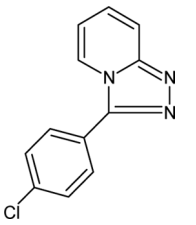
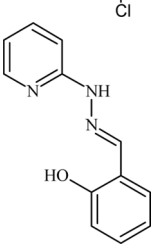
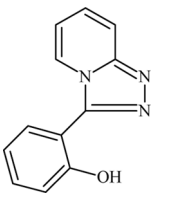
Procedure for Preparation of 2-Hydrazine Pyridine (2)

2-Chloropyridine (20 mmol) was mixed with hydrazine hydrate (5 vol), and the resultant mixture was heated under reflux in an oil bath for 6 h. The reaction was

Table 3. Synthesis of 1,2,4-triazolo[4,3-a]pyridine from heterocyclic hydrazones by using [bis-(trifluroacetoxy)iodo]benzene

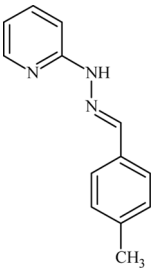
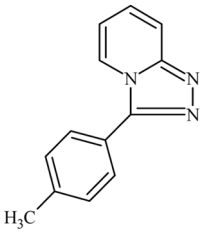
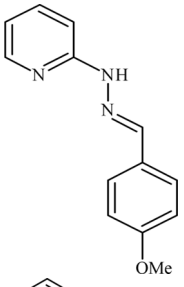
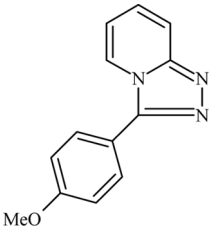
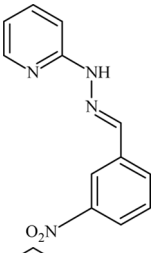
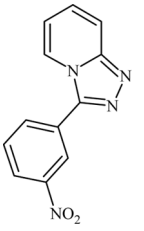
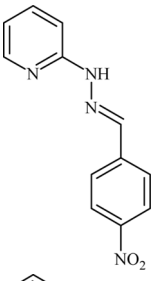
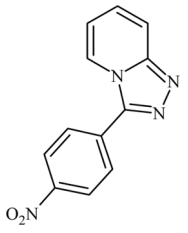
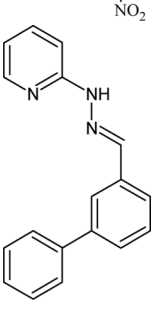
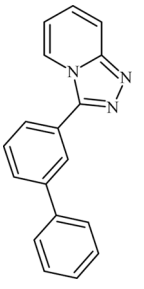


4a-4p *5a-5p*

Entry	Hydrazones	Product	Yield (%)
a			94
b			91
c			94
d			89

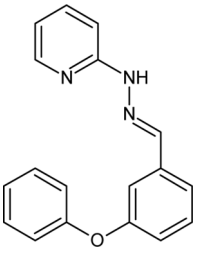
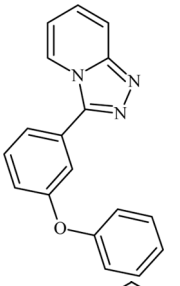
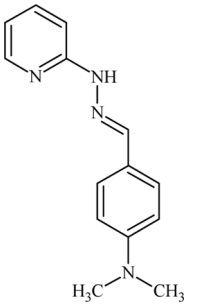
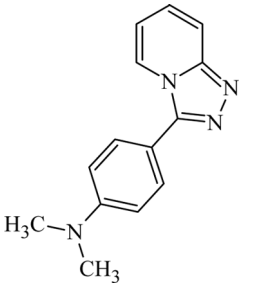
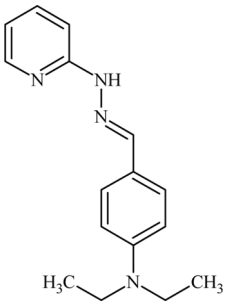
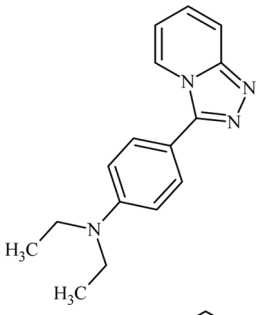
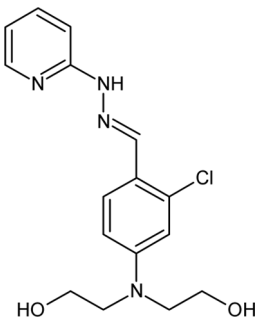
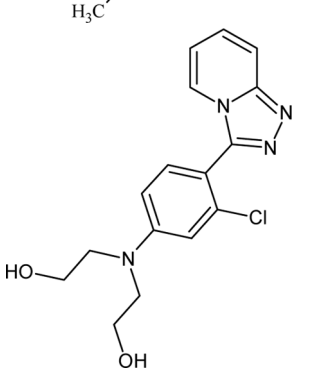
(*Continued*)

Table 3. Continued

Entry	Hydrazones	Product	Yield (%)
e			91
f			87
g			93
h			95
i			88

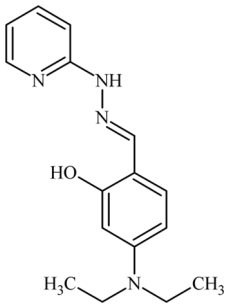
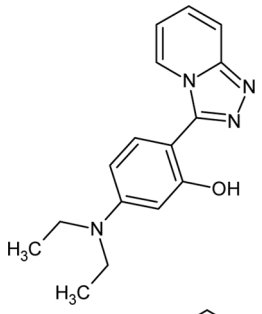
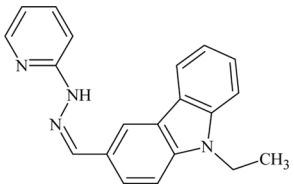
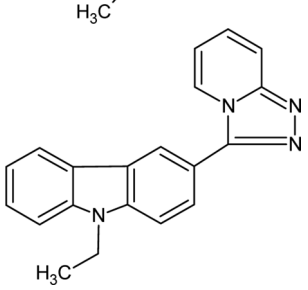
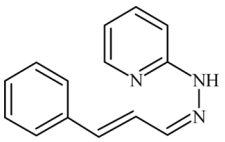
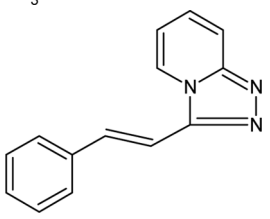
(*Continued*)

Table 3. Continued

Entry	Hydrazones	Product	Yield (%)
j			85
k			91
l			90
m			84

(*Continued*)

Table 3. Continued

Entry	Hydrazones	Product	Yield (%)
n			88
o			94
p			96

[a]Reagents and reaction conditions: Hydrazones (10 mmol), [bis-(trifluroacetoxy)iodo]benzene (11 mmol); solvent: anhydrous dichloromethane; temperature: room temperature; time: 10 min.

[b]Isolated yield after crystallization and structure were confirmed by ^{1}H NMR spectra and physical constants.

monitored by TLC. After the completion of the reaction, the reaction mixture was cooled and extracted with diethyl ether (2 × 20 mL). The organic layer was dried over anhydrous sodium sulfate and kept in the freezer. A white crystalline powder of the product was obtained. Yield 79%, mp 45 °C (lit. 45–46 °C).

General Procedure for Preparation of Heterocyclic Hydrazones (4a–p)

2-Hydrazinopyridine (**2**) (10 mmol) was dissolved in a boiling ethanol (10 mL), and the different substituted aldehydes (**3a–p**) (10 mmol in 10 mL ethanol), were added dropwise to the solution. After that, the solution was stirred and heated under reflux for 20 min. The hydrazones (**4a–p)** formed were filtered from the cooled solution and used in the next reaction without purification.

General Procedure for Preparation of 1,2,4-Triazolo[4,3-a]pyridines (5a–p)

Hydrazones **(4a–p)** (10 mmol) was dissolved in dichloromethane (10 mL), [bis(trifluroacetoxy)iodo]benzene (11 mmol) was added, and the reaction mixture was stirred at room temperature for 10 min. After completion of the reaction, the reaction mixture was diluted with dichloromethane (10 mL) and washed successively with 10% sodium bisulfate solution (2×20 mL), 10% sodium bicarbonate solution (2×20 mL), and water (2×20 mL). The organic layer obtained was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was further crystallized from ethanol to afford the product.

Representative Spectral Data

3-Phenyl-[1,2,4]triazolo[4,3-a]pyridine (Table 3, entry *a*). ^{1}H NMR (400 MHz) δ 7.12 (t, 1H), 7.56–7.62 (m, 4H), 7.87–7.94 (m, 3H), 8.59 (m, 1H); mp 174 °C; HPLC purity: 99.87%.

3-(4-Chlorophenyl)[1,2,4]triazolo[4,3-*a*]pyridine (Table 3, entry *c*). ^{1}H NMR (400 MHz) δ 7.21 (d, 2H), (7.25–7.48, m, 4H), 7.84 (m, 1H), 7.52 (m,1H), 8.68 (d, 1H); mp 132 °C; HPLC purity: 99.31%.

3-(4-Methylphenyl)[1,2,4]triazolo[4,3-*a*]pyridine (Table 3, entry *e*). ^{1}H NMR (400 MHz) δ 2.43 (s, 3H), 7.23 (d, 2H), 7.41 (d, 2H), 8.65 (d, 2H), 7.83 (m, 1H), 7.43 (m, 2H); mp 152 °C; HPLC purity: 98.89%.

3-(4-Methoxyphenyl)[1,2,4]triazolo[4,3-*a*]pyridine (Table 3, entry *f*). ^{1}H NMR (400 MHz) δ 3.83 (3H, s), 6.92 (d, 2H), 7.43 (d, 2H), 8.61 (d, 1H), 7.81 (m, 1H), 7.45 (m, 2H); mp: 125 °C; HPLC purity: 99.08%.

3-(3-Nitrophenyl)[1,2,4]triazolo[4,3-*a*]pyridine (Table 3, entry *g*). ^{1}H NMR (400 MHz) δ 7.01 (m,1H), 7.37 (m, 1H), 7.87 (m, 2H), 8.32 (m, 2H), 8.58 (m, 2H); mp 290 °C; HPLC purity: 99.45%.

***N,N*-Dimethyl-4-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)aniline (Table 3, entry *k*).** ^{1}H NMR (400 MHz) δ 2.96 (s, 6H), 6.87 (d, 2H), 7.19 (m,1H), 7.64 (m, 3H), 7.97 (d, 1H), 8.57 (d, 1H); mp 192 °C; HPLC purity: 98.86%.

9-Ethyl-3-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-9*H*-carbazole (Table 3, entry *o*). ^{1}H NMR (400 MHz) δ 1.63 (s, 3H), 3.94 (q, 2H), 7.43 (d, 1H), 7.13 (m, 1H), 7.02 (m, 1H), 7.62 (d, 2H), 7.30 (d, 2H), 7.43 (d, 1H), 8.64 (d, 1H), 7.43 (m, 2H); mp 167 °C; HPLC purity: 99.23%.

3-[(*E*)-2-Phenylethenyl][1,2,4]triazolo[4,3-*a*]pyridine (Table 3, entry *p*). ^{1}H NMR (400 MHz) δ 6.99 (d, 1H), 6.76 (d, 1H), 7.24–7.43 (m, 6H), 8.69 (d, 1H), 7.85 (d, 1H), 7.58 (m, 1H); mp 169–171 °C; HPLC purity: 99.57%.

ACKNOWLEDGMENT

The author is thankful to Indian Institute of Technology Mumbai, for providing the ^{1}H NMR facility.

REFERENCES

1. (a) McMlure, K. F.; Abramov, Y. A.; Laird, E. R.; Barberia, J. T.; Cai, W.; Carty, T. J.; Cortina, S. R.; Danley, D. E.; Dipesa, A. J.; Donahue, K. M.; Dombroski, M. A.; Elliott, N. C.; Gabel, C. A.; Han, S.; Hynes, T. R.; Lemotte, P. K.; Mansour, M. N.; Marr, E. S.; Letavic, M. A.; Pandit, J.; Ripin, D. B.; Sweeney, F. J.; Tan, D.; Tao, Y. Theoretical and experimental design of atypical kinase inhibitor: Application to P_{38} MAP kinase. *J. Med. Chem.* **2005**, *48*, 5728–5737; (b) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Buddu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. Potent 1,3,4-trisustituted pyrrolidin CCR_5 receptor antagonists: Effect of fused heterocycles on antiviral activity and pharmacokinetic properties. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129–2134; (c) Sarges, S.; Howard, H. R.; Browne, R. G.; Label, L. A.; Seymour, P. A.; Koe, B. K. 4-Amino[1,2,4]triazolo[4,3-a]quinoxalines: A novel class of potent adenosine receptors antagonists and potential rapid onset antidepressant. *J. Med. Chem.* **1990**, *33*, 2240–2254; (d) Brown, D. J.; Iwai, Y. Purine analogues as amplifiers of phleomycin, VI: The synthesis of some benzothiazole, benzoxazole, and s-triazolo pyrimidine amplifiers. *Aust. J. Chem.* **1979**, *32*, 2727–2733.
2. Bower, J. D.; Doyle, E. P. Preparation of fused triazole system. *J. Chem. Soc.* **1957**, 727–732.
3. Pollak, A.; Tisler, M. Synthesis of pyridazine derivatives, V: Formation of s-triazolo-(4,3-b)-pyridazines and bis-s-triazolo-(4,3-b,3′,4′-f)-pyridazines. *Tetrahedron* **1966**, *22*, 2073–2079.
4. Gibson, M. S. Hydrazones IV: The bromination of benzylidene 2-pyridylhydrazone. *Tetrahedron* **1963**, *19*, 1587–1589.
5. Naqui, S.; Srinivasan, K. R. Two improved oxidation procedure for the synthesis of some fused s-triazoles. *J. Sci. Ind. Res.* **1962**, *21B*, 456–457.
6. Wang, Y.; Sarris, K.; Sauer, R. D.; Djuric, S. W. A simple and efficient automatable one-step synthesis of triazolopyridines from carboxylic acids. *Tetrahedron Lett.* **2007**, *48*, 2237–2240.
7. Sanana, A. K.; Mirza, Y.; Aneja, K. R.; Prakash, O. Hypervalant iodine–mediated synthesis of 1-aryl/hetryl-1,2,4-triazolo[4,3-a]pyridine and 1-aryl/hetryl-5-methyl-1,2,4-triazolo[4,3-a]quinoline as antibacterial agent. *Eur. J. Med. Chem.* **2003**, *38*, 533–536.
8. Bourgeois, P.; Cantegril, R.; Chene, A.; Gelin, J.; Mortier, J.; Moyroud, A. Improved synthesis of 3-substituted 1,2,4-triazolo[4,3-a]pyridines and 1,2,4-triazolo[4,3-a]pyridazines. *J. Synth. Comm.* **1993**, *23*, 3195–3199.
9. Crljenak, S.; Tabakovic, I.; Jeremic, D.; Gaon, I. Electrochemical synthesis of heterocyclic compounds, XV: Anodic synthesis of s-triazolo[4,3-a]pyridine derivatives. *Acta Chem. Scand.* **1983**, *B37*, 527–535.
10. (a) Zhdankin, V. V.; Stang, P. Recent development in the chemistry of polyvalent iodine compounds. *J. Chem. Rev.* **2002**, *102*, 2523–2584.
11. Zhdankin, V. V. Benziodoxole-based hypervalant iodine reagents in organic chemistry. *Curr. Org. Synth.* **2005**, *2*, 121–125.
12. Du, Y.; Liu, R.; Linn, G.; Zhao, K. Synthesis of N-substituted indol derivatives via PIFA-mediated intramolecular cyclization. *Org. Lett.* **2006**, *8*, 5919–5922.

13. Tellitu, I.; Serana, S.; Herrero, M. T.; Moreno, I.; Dominguez, E.; San Martin, R. Intramolecular PIFA-mediated alkynes amidation and carboxylation. *J. Org. Chem.* **2007**, *72*, 1526–1529.
14. Fleming, F.; Funk, L.; Altundas, R.; Tu, Y. Deprotecting dithiane containing alkaloids. *J. Org. Chem.* **2001**, *66*, 6502–6504.
15. Moriarty, R. M.; Berylund, B. A.; Penmasta, R. Direct α-hydroxylation of ketones under acidic conditions using [bis(trifluoroacetoxy)]iodobenzene. *Tetrahedron Lett.* **1992**, *33*, 6065–6068.
16. Talvekar, V. N.; Takale, B. S.; Bachhav, H. M. Simple and facile method for the preparation of vinyl azides. *Tetrahedron Lett.* **2009**, *50*, 5056–5058.