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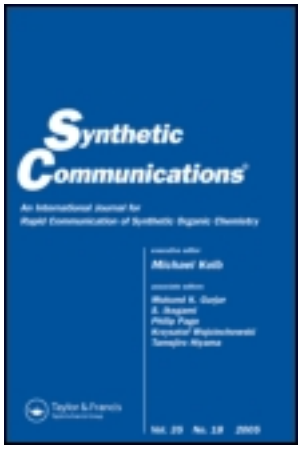

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Iodine-Catalyzed, Efficient, One-Pot Protocol for the Conversion of Araldehydes into 5-Aryl-1H-tetrazoles

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IODINE-CATALYZED, EFFICIENT, ONE-POT PROTOCOL FOR THE CONVERSION OF ARALDEHYDES INTO 5-ARYL-1*H*-TETRAZOLES

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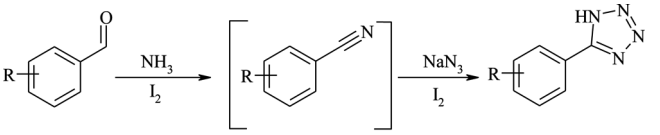
GRAPHICAL ABSTRACT



R= -H, -Cl, -OH, $-CH_3$, $-OCH_3$,- NO_2, -CHO

7-12h, 65-90% yield

Abstract *An easy access to various 5-aryl-1*H*-tetrazoles by a one-pot direct conversion of aldehydes to tetrazoles without the isolation of the intermediate nitriles using commercially available iodine as a catalyst is described. The protocol offers advantages in terms of good yields, mild reaction conditions, short reaction times, and use of readily available environmentally compatible catalyst.*

Keywords Ammonia; araldehydes; 5-aryl-1*H*-tetrazoles; iodine; sodium azide

INTRODUCTION

Synthesis of tetrazoles has been a subject of intense investigation because of their broad application in different scientific research fields.[1,2] Derivatives of tetrazoles are useful as antiviral, antibacterial, antifungal, and antituberculous agents.[3a] In addition to this, tetrazoles are used as catalysts in the synthesis of phosphonates.[3b] Fang and coworkers used a series of primary alcohols and aldehydes with iodine in ammonia–water to get the intermediate nitriles, which without isolation were subjected to a [2 + 3]-cycloaddition reaction with dicyandiamide and sodium azide in presence of $ZnBr_2$ to afford the corresponding triazines and tetrazoles at reflux[4] and under microwave irradiation.[5] These method suffer from long reaction times and harsh reaction conditions. These are the only two methods available in the literature for this one-pot, two-step synthesis of tetrazoles from aldehydes. Thus development of a catalytic synthetic method for the preparation of tetrazoles still remains an

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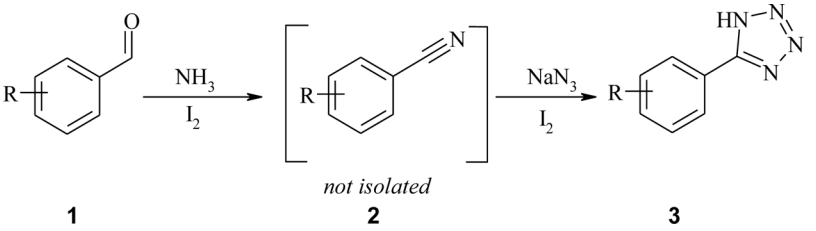

Scheme 1. Formation of tetrazole from aldehyde.

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active research area, and in continuation of our work on the development of efficient and environmentally friendly methods for the catalytic synthesis of bioactive molecules and heterocycles, we have synthesized a number of heterocycles using iodine as catalyst, few of which include the synthesis of azalactones,[6] α,α′-bis(arylmethylidene) cycloalkanones,[7] β-acetamido-β-aryl-propiophenones,[8] and xanthenes.[9] Looking into the utility of iodine as catalyst, its cost, availability, and environmental compatibility, we decided to employ iodine alone for the synthesis of tetrazoles from aldehydes by a one-pot, two-step reaction, without isolating the intermediate nitriles (Scheme 1).

RESULTS AND DISCUSSION

Our investigation began with the evaluation of I_2 as reagent for the synthesis of 5-(4-methoxyphenyl)-1*H*-tetrazole from 4-methoxybenzaldehyde without isolating the corresponding 4-methoxybenzonitrile at 100 °C in tetrahydrofuran (THF) as a solvent. The use of 1 equivalent of I_2 (for two steps) afforded 73% of the desired product. Optimization of the reaction condition was undertaken to increase the yield of the product using different amounts of I_2. The yield was increased to 84% using $1 + 1 = 2$ equivalent of I_2 under solvent-free conditions. However, the addition of $1 + 2$ or $2 + 1$ equivalents of the I_2 did not improve the yield further. We next examined a wide variety of araldehydes to establish the scope of this transformation. Araldehydes with electron-withdrawing groups as well as electron-donating substituents underwent this one-pot conversion to give the corresponding tetrazoles in good yield (Table 1). In general, the aldehyde was first treated with ammonia–water and THF in the presence of I_2, Once the formation of nitrile was confirmed by thin-layer chromatography (TLC), NaN_3 was then added to the same flask to get the corresponding 5-aryl-1*H*-tetrazoles (**3**). In all cases, the reactions proceeded efficiently at 100 °C.

Caution: Use of *excess* ammonia in combination with sodium azide or iodine in the following procedure should be avoided because of the release of traces of hazardous hydrazoic acid or nitrogen triiodide monoamine.[10,11]

EXPERIMENTAL

All chemicals used were commercial and all solvents were distilled before use. Reactions were monitored on TLC by comparison with the authentic samples. Melting points were determined on a Büchi melting-point apparatus. The products were characterized by comparison of their physical data with those of known samples or by

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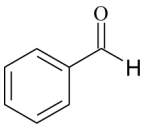
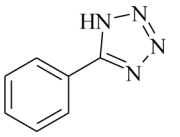
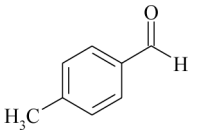
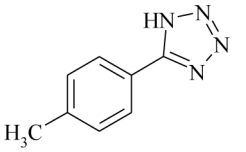
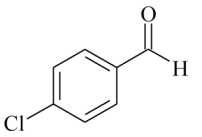
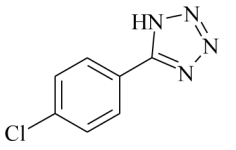
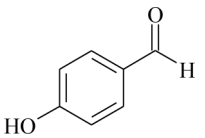
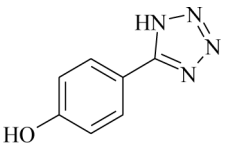
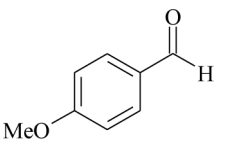
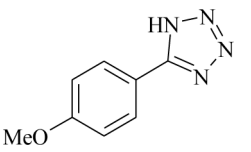
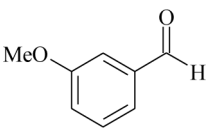
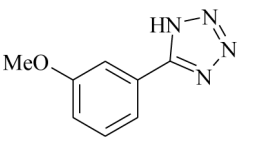
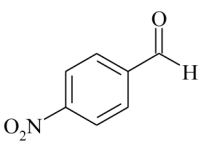
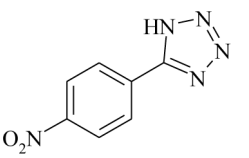
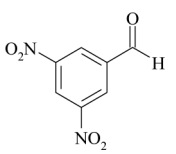
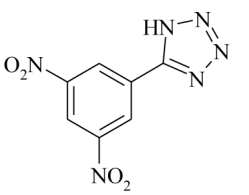
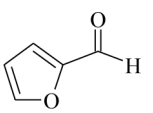
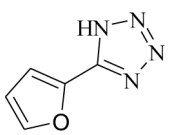
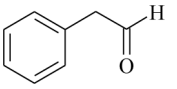
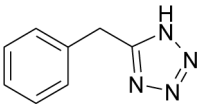
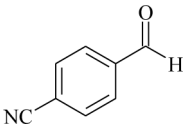
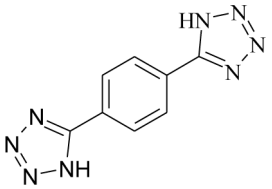
Table 1. Synthesis of tetrazoles from aromatic aldehydes using molecular iodine

Entry	Aldehyde (**1**)	Tetrazole (**3**)[a]	Time (h)	Yield (%)[b,c]
a			8	90
b			12	89
c			8	85
d			10	79
e			9	84
f			8.5	79
g			7	81
h			8	67
i			7	90

(*Continued*)

Table 1. Continued

Entry	Aldehyde (**1**)	Tetrazole (**3**)[a]	Time (h)	Yield (%)[b,c]
j			12	65
k			8.5	73

[a]All reactions were performed using an aldehyde (5 mmol), sodium azide (6 mmol), and I_2 (2equivalents).
[b]Isolated yield.
[c]All the products are known, and physical properties agree with the literature values.

comparison of their infrared (IR), ^{1}H NMR, gas chromatography (GC)–mass, and liquid chromatography (LC)–mass spectra. The IR and ^{1}H NMR spectra of the products were recorded on Shimatzu Fourier transform (FT)–IR 8400 and Bruker AMX (400-MHz) spectrometers respectively. GC-MS analysis was performed on a Shimatzu QP5050A series instrument. Yields refer to the isolated yields of the products.

General Procedure for the Preparation of 5-Substituted 1*H*-Tetrazole

A mixture of an appropriate aldehyde (**1,** 5 mmol), iodine (5 mmol), liquid ammonia (5 mmol, 28% solution), and THF (5 mL) was stirred at room temperature for about 1 h. When the dark solution became colorless, NaN_3 (6 mmol) and iodine (5 mmol) were then added, and the reaction mixture was heated to 100 °C for 7–12 h with vigorous stirring. The crude reaction mixture was transferred into a separating funnel, and ethyl acetate (50 mL) was added. The pH was adjusted to 1.0 with HCl. Traces of I_2 were removed by washing the organic phase with a sodium thiosulphate solution (3×10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to get pure 5-aryl-1*H*-tetrazole (**3**) in 65–90% yield.

CONCLUSION

A facile, convenient, and less hazardous synthetic method for the synthesis of 5-substituted-1*H*-tetrazoles in good yields and high purity from various araldehydes is achieved. This method offers several advantages including mild reaction conditions, low catalyst loading, and no isolation of the intermediate. In addition, our process involves use of one environmentally benign, cheap, and easy-to-handle catalyst.

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