HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 2: (3), 2012, 277-282**

PHOSPHORUS PENTOXIDE-METHANESULFONIC ACID CATALYZED EFFICIENT SYNTHESIS OF 5-SUBSTITUTED 1*H*-TETRAZOLE DERIVATIVES

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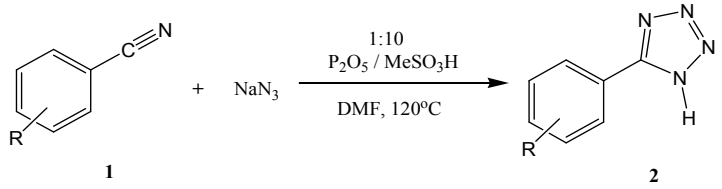
ABSTRACT
The mixture of phosphorus pentoxide-methanesulfonic acid (Eaton's reagent) is prove to be an efficient protocol for the [3+2] cycloaddition reaction between sodium azide and organic nitriles to give the corresponding 5-substituted 1*H*-tetrazole derivatives in good to excellent yields. The in situ formation of hydrazoic acid helps for the [3+2] cycloaddition reaction providing 5-substituted 1*H*-tetrazole with short reaction time.

KEYWORDS
[3+2] cycloaddition, sodium azide, 5-substituted 1*H*-tetrazoles, hydrazoic acid, Eaton's reagent.

INTRODUCTION
Recently, considerable interest in tetrazole derivatives has occurs in publications due to their wide range of applications in material sciences,[1] pharmaceuticals,[2] synthesis of non-covalent complexes,[3] and beyond all, high-energy substances.[4] The tetrazoles played an important role in medicinal chemistry, a metabolically stable surrogate are often encountered as a bioisosteres of carboxylic acids in biologically active molecules,[5] also act as antiallergic, anti-inflammatory, antipemilic, antimicrobial, stimulants or sedatives on the central nervous system.[6] In addition, these compounds have a significant role as oxidizers and plant growth regulators.[7] Furthermore, tetrazole compounds are important precursors for synthesis of various nitrogen containing heterocycles and many useful transformation.[8] The acid catalyzed [3+2] cycloaddition reaction between hydrazoic acid and organic nitriles is method of choice for the preparation of tetrazoles, however this efficient method serves from disadvantage of producing a highly toxic and volatile hydrazoic acid in large extent,[9] therefore it was decided to develop facile method for the synthesis of 5-substituted 1*H*-tetrazoles as using Eaton's reagent as a mild acid catalyst. Several methods for the synthesis of 5-substituted 1*H*-tetrazole have been reported through [3+2] cyclocondensation of sodium azide and nitriles in the presence of catalyst such as Mont K-10 clay,[10a] Zn/Al hydrotalcite,[10b] ZnO,[10c] $FeCl_3$-SiO_2,[10d] Amine salts,[10e] Sb_2O_3,[10f] CoY,[10g] $AlCl_3$,[10h] Zn (II) salts,[10i] $ZnCl_2$,[10j] Cu_2O.[10k] Recently, Du [11] and Yamamoto[12] reported the acid catalyzed facile synthesis of 5-substituted and 1-substituted tetrazoles using silica supported sulfuric acid and hydrochloric acid respectively. The major constituent in Eaton's reagent is methanesulfonic acid have advantages over these such as unlike sulfuric acid, methanesulfonic acid is non-

oxidizing have same acid strength as that of sulfuric acid, thus leading to higher yields in many reactions and unlike hydrochloric acid methanesulfonic acid forms no toxic fumes even at very high concentration and is less corrosive.

In continuation of our work on the development of new methods for the synthesis of 5-substituted 1*H*-tetrazol.[13] Herein, we report an efficient protocol from a wide variety of organic nitriles with sodium azide using a mixture of phosphorus pentoxide-methanesulfonic acid under mild conditions (Scheme 1).



1 **2**

Scheme 1. Synthesis of 5-substituted 1*H*-tetrazoles using Eaton's reagent.

Eaton's reagent (1:10 phosphorus pentoxide in methanesulfonic acid) is an inexpensive and commercially available substance synthesized by Philip E. Eaton in 1973, found to be a good alternative to polyphosphoric acid. Which can be used to overcome the disadvantages of polyphosphoric acid as a catalyst for dehydration reactions, because it has a much lower viscosity, it is easier to handle and no complex separation procedures need to be employed. Combination of phosphorus pentoxide and methanesulfonic acid ($P_2O_5/MeSO_3H$) can also be employed as catalyst for Fisher-Indole synthesis, Beckmann rearrangement and Schmidt rearrangement processes.[14] Many processes that employ a mixture of $P_2O_5/MeSO_3H$ are not only more economical, they are also more environmentally friendly and offers a number of distinct advantages such as safe in industrial scale, low environmental impact, chlorine free, easy work-up procedures, rapid reactions and high purity products with excellent yields. The distinctive physical and chemical properties of Eaton's reagent make it very useful substance in many different reactions with different applications. We recently use this reagent for synthesis of Bis(indolyl)methanes under mild conditions, we found that reagent works extremely well for the coupling reaction.[15]

RESULT AND DISCUSSION

Herein, we report for the first time that mixture of $P_2O_5/MeSO_3H$ can be an effective and high yielding protocol for [3+2] cycloaddition of sodium azide and organic nitriles to yield 5-substituted 1*H*-tetrazoles with short reaction time. Eaton's reagent is colorless, odorless liquid mixture of non oxidizing methanesulfonic acid and a powerful dehydrating agent phosphorus pentoxide. The addition of phosphorus pentoxide increases the solubility of organic compounds in methanesulfonic acid; this was introduced by Eaton and has been used enormously in organic synthesis.

Initially, the reaction of benzonitrile and sodium azide was selected as a model reaction to optimize the reaction conditions and the obtained results are listed in Table 1. Not many organic solvents are stable at the high temperature necessary for cycloaddition reaction, and for this reason DMF is most commonly used for this purpose. First we optimized the amount of

$P_2O_5/MeSO_3H$ required in the [3+2] cycloaddition reaction between sodium azide and benzonitrile using DMF as solvent at 120^oC. Using 1 mmol of $P_2O_5/MeSO_3H$ product obtained in moderate yield (Table 1, Entry 1, 60%). The optimum results are obtained when 2 mmol of $P_2O_5/MeSO_3H$ used (Table 1, Entry 2, 85%) providing the desired product in excellent yield with less reaction time. Further increasing the amount of $P_2O_5/MeSO_3H$ decreases the yield with prolonged reaction time (Entries 3, 4 and 5). When reaction was performed by using 5 mmol of $P_2O_5/MeSO_3H$, reaction was not completed even after 48 h (Entry 5). Therefore, we found that 2 mmol of $P_2O_5/MeSO_3H$ was sufficient to push the reaction into completion with high yield in short reaction time. For comparison, we use P_2O_5 and $MeSO_3H$ separately in DMF at 120^0C for this transformation, results shows that both reaction gives moderate yields and takes long time for completion (Entries 6 and 7). Next we performed this reaction without $P_2O_5/MeSO_3H$ using the same solvent (Entry 8), no reaction take place even after 48 h. Solvent has pronounced effect in these reactions (Table 1, Entries 2, 9 and 10) where DMF, DMSO gave well and moderate yields respectively, therefore DMF found to be the most preferred solvent for this reaction, but THF is not suitable solvents for this reaction.

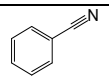
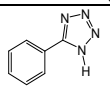
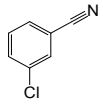
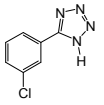
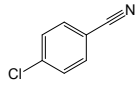
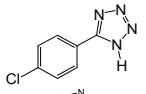
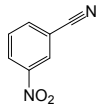
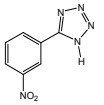
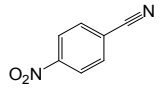
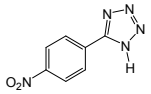
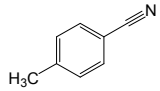
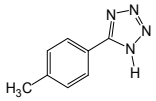
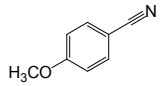
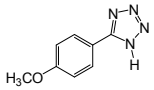
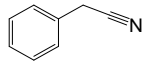
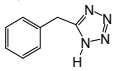
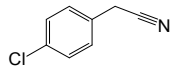
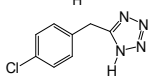
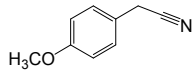
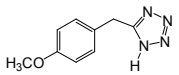
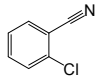
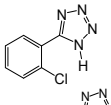
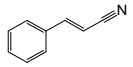
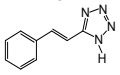
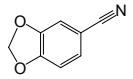
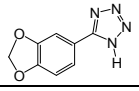
Table 1. Optimization of reaction conditions on the formation of 5-phenyl-1*H*-tetrazole[a].

Entry	Catalyst	Ratio (mmol)	Solvent	Time (h)	Yield (%)[b]
1	$P_2O_5/MeSO_3H$	1	DMF	6	60
2	$P_2O_5/MeSO_3H$	2	DMF	4	85
3	$P_2O_5/MeSO_3H$	3	DMF	5	75
4	$P_2O_5/MeSO_3H$	4	DMF	10	65
5	$P_2O_5/MeSO_3H$	5	DMF	48	30[c]
6	P_2O_5	2	DMF	9	69
7	$MeSO_3H$	2	DMF	9	65
8	No catalyst	--	DMF	48	Trace[d]
9	$P_2O_5/MeSO_3H$	2	DMSO	9	51
10	$P_2O_5/MeSO_3H$	2	THF	48	Trace[d]

[a]Reaction conditions - Eaton's reagent (2 mmol), Nitrile (5 mmol), NaN_3 (7.5 mmol), DMF (10 mL) at 120^oC. [b]Isolated Yield. [c]Incomplete conversion even after 48 h. [d]Product could not be isolated.

After an optimization study, various organic nitriles as a substrate are used to investigate the generality and applicability of this method using $P_2O_5/MeSO_3H$; results are summarized in Table 2. Among all studied examples, most of nitriles gave good yields over 75%. Nitrile with different substituent showed different reaction activity. It is evident that there is a highly influential steric factor, para-substituted benzonitrile afforded higher conversion rates with short reaction times as compared with the ortho analogue. For example, 4-chlorolbenzonitrile converted to the corresponding tetrazole in excellent yield (94 %) in only 2 h (Table 2, Entry 3), while the ortho-derivative rendered only 74% yield with more reaction time (Table 2, Entry 11). Nitrile with electron withdrawing group gives the highest yields with shorter reaction time (Table 2, Entries 2-5 and 9) and *para* substituted nitriles with electron donating groups provide corresponding tetrazoles in moderate to good yields with slightly more reaction time (Entries 6, 7 and 10). Cinnamonitrile and Piperonylonitrile give minimum and moderate yields respectively with long reaction time (Table 2, Entries 12 and 13).

Table 2. Eaton's reagent catalyzed synthesis of 5-substituted 1*H*-tetrazoles **2**[a]

Entry	Substrate (1)	Product (2)	Time (h)	Yield (%)[b]
1			4	85
2			2	90
3			2	92
4			4	90
5			4	91
6			6	84
7			6	86
8			8	70
9			6	81
10			8	73
11			9	74
12			18	68
13			16	74

[a]Reaction conditions - Eaton's reagent (2 mmol), Nitrile (5 mmol), NaN_3 (7.5 mmol), DMF (10 mL) at 120°C.
[b]Isolated Yield.

EXPERIMENTAL

All solvents and chemicals were commercial and used without further purification. Eaton's reagent (7.7/92.3 % by weight of P_2O_5/$MeSO_3H$) was purchased from Sigma-Aldrich. Melting points were recorded in open capillaries. The purity of the compounds was checked by TLC on silica gel G (Merck). ^1H spectra were scanned in DMSO-d_6 on bruker (300 MHz) and Varian mercury plus-400 (400 MHz) spectrometer taking TMS as an internal standard for both the spectrometers. IR spectra were recorded on Shimadzu FT-IR Affinity-1 spectrometer using KBr

discs. Mass spectra (ESI-MS) were recorded on VG AUTOSPEC mass spectrometer. The products were purified by recrystallization using ethanol.

Typical procedure for the synthesis of 5-substituted 1H-tetrazoles –
Eaton's reagent (2 mmol) was added to a mixture of benzonitrile (5 mmol), sodium azide (7.5 mmol) in DMF (10 mL) and stirred at 120^0C for 4 h. After completion of the reaction (monitored by TLC) pour the content into ice cold water (50-60 mL) after which it was acidified with conc. HCl (pH 4-5), the product precipitate out was collected by filtration, washed it with sufficient water and dried to afford crud 5-phenyl-1*H*-tetrazole, recrystalized from ethanol, provided 5-phenyl-1*H*-tetrazole as crystalline white solid. Yield - 92 %, mp- 216-218^0C.

Spectral data for the selected compounds-
5-phenyl-1*H*-tetrazole (1) *[10i]* **:** Mp = 216-218^0C; IR (KBr, cm^{-1}): 3128, 3076, 2981, 2839, 2611, 1608, 1564, 726; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.57-7.61 (m, 3H), 8.01-8.04 (m, 2H); MS *(m/z)*: 147 (M^++H).
5-(4-chlorophenyl)-1*H*-tetrazole (3) *[10j]***:** Mp = 264-266^0C; IR (KBr, cm^{-1}): 3068 , 2997, 2426 , 1610, 1489, 1436, 831; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.7 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* =8.8 Hz, 2H); MS-EI *(m/z)* = 179 [M^+-H].
5-p-tolyl-1*H*-tetrazole (6) *[10i]* **:** Mp = 248-250^0C; IR (KBr, cm^{-1}): 3120, 2980, 2908, 1610, 1564, 1487, 1435, 831; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.36 (s, 3H), 7.38 (d, 2H, *J* = 7.8 Hz), 7.90 (d, 2H, *J* = 8.1 Hz); MS *(m/z)*: 161 (M^++H).
5-(4-methoxyphenyl)-1*H*-tetrazole (7) *[10k]***:** Mp = 230-232^0C ; IR (KBr, cm^{-1}): 3078, 2983, 1612, 1500, 1267, 1182 , 835; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 3.85 (s, 3H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 8.8 Hz, 2H); MS-EI *(m/z)* = 177 [M^++H].
5-benzyl-1*H*-tetrazole (8) *[10j]***:** Mp= 120-122^0C ; IR (KBr, cm^{-1}): 3078, 2962, 1608, 1542, 698; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 4.28 (s, 2H), 7.25-7.27 (m, 3H), 7.31-7.35 (m, 2H); MS-EI *(m/z)* = 160 [M^+H].
5-(4-methoxybenzyl)-1*H*-tetrazole (10) *[13]* **:** Mp = 156-158^0C; IR (KBr, cm^{-1}): 3035, 3012, 2966, 1612, 1556, 1463, 1176, 1028, 825; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.69 (s, 3H), 4.19 (s, 2H), 6.87 (d, 2H, *J*= 8.4 Hz), 7.17 (d, 2H, *J*= 8.4 Hz); MS *(m/z)*: 191 (M^++H).
5-(3-chlorophenyl)-1*H*-tetrazole (11) *[13]* **:** Mp = 110-114^0C; (KBr, cm^{-1}): 3068, 2968, 2430, 1558 , 1473, 891; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.45-7.52 (m, 2H), 8.0 (d, *J* = 7.6 Hz, 1H), 8.12 (s, 1H); IR MS-EI *(m/z)* = 179 [M^--H].
5-styryl-1*H*-tetrazole (12): Mp = 172-174^0C; IR (KBr, cm^{-1}): 3196, 2985, 2835, 1649; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.28-7.70 (m, 7H); MS *(m/z)*: 173 (M^++H).
5-(benzo[d][1,3]dioxol-6-yl)-1*H*-tetrazole (13): Mp = 252-254^0C; IR (KBr, cm^{-1}): 3064, 2997, 2899, 2621, 1600, 1490, 1253, 1043, 927; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 6.12 (s, 2H), 7.11 (d, 2H, *J*= 8.1 Hz), 7.48 (s, 1H), 7.55 (d, 2H, *J*= 8.1 Hz); MS *(m/z)*: 191 (M^++H).

CONCLUSION
In summary, we have developed for the first time that the use of Eaton's reagent as liquid catalyst for an efficient, high yielding method for the synthesis of 5-substituted 1*H*-tetrazoles via [3+2] cycloaddition.. The present method which makes use of commercially available Eaton's reagent offers very attractive features such as simple operations, mild reaction condition and excellent yields with shorter reaction time.

ACKNOWLEDGMENTS

MNP is thankful to UGC, New Delhi for SAP-RFSMS fellowship. Authors are also thankful to Prof P. P. Mahulikar - Director, School of Chemical Sciences, North Maharashtra University, Jalgaon for providing necessary facilities.

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Received on May 11,2012.