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$InCl_3$-Catalyzed [2+3] Cycloaddition Reaction: A Rapid Synthesis of 5-Substituted 1*H*-tetrazole under Microwave Irradiation

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Abstract: A series of 5-substituted 1*H*-tetrazole were efficiently prepared by $InCl_3$ catalyzed (10 mol %) from structurally divert organic nitriles with sodium azide under the influence of microwave irradiation. The present protocol was successfully applied to the aliphatic, aryl, benzylic and heterocyclic nitriles and corresponding 5-substituted 1*H*-tetrazole were obtained in good to excellent yield (70-96%). This method gives remarkable advantages such as short reaction time, simple work-up procedure and economical beneficial.

Key words: $InCl_3$, Nitriles, [2+3] cycloaddition, 5-Substituted 1*H*-tetrazole, Microwave irradiation.

Introduction

The growing interest in heterocyclic compounds and their methods for synthesis are of paramount importance to medicinal, chemical and agricultural research because they make novel materials with unique properties. In recent years, attention towards synthesis of tetrazole and its analogues has been constantly increased because of a number of highly efficient drugs based on tetrazole.[1] Tetrazole compounds have broad range of pharmaceutical applications[2] as antiallergic, anti-inflammatory, antipemilic, antimicrobial and act as stimulants or sedatives on the central nervous system. They also used as trigger explosives, components of mixed propellants and gas-generating compositions.[3] In addition, these compounds have a significant role as oxidizers and plant growth regulators.[4] Furthermore, tetrazole compounds are significant precursors for synthesis of various nitrogen containing heterocycles and many useful transformation.[5] Particularly, 5-substituted 1*H*-tetrazole were conveniently prepared by direct [2+3] cycloaddition between a nitrile and an azide.[6] Many synthetic methods were reported for this transformation, requires amine salts[7], strong lewis acid[8], expensive and toxic metals[9] by in situ generated hydrazoic acid which is highly toxic and explosive. Recently, Sharpless and co-workers reported an innovative and safe procedure for the synthesis of tetrazoles using stoichiometric amounts of

Zn (II) salts in water.[10] However, many of the established approaches for this [2+3] cycloaddition reaction are still severely limited in their use by the lack of generality, the harsh reaction conditions such as high temperatures and long reaction times, or the multistep procedures required.

Encouraged by the intense research activity in the field of tetrazole and in pursuit of our continuing interest in developing greener methodologies by using microwave irradiations and metal salts[11a], we envisioned the synthesis of 5-substituted 1*H*-tetrazole by milder lewis acid under the microwave influence. Microwave assisted organic reaction[11b] currently gaining popularity due to many advantages such as great selectivity, enhanced reaction rates, economical beneficial, short reactions time, operational simplicity with minimal stockpiling of chemicals and avoiding transportation of hazardous substances. These increasing demands offer many opportunities for microwave chemistry in the development of environmentally benign methods for the preparation of intermediated, speciality chemicals and pharmaceuticals.[12] Recently, indium (III) chloride was emerged as a powerful lewis acid catalyst imparting high region- and chemoselectivity in various transformations.[13] For instance, Indium(III) chloride are effectively used in promoting the Diels-Alder reaction,[14] cycloaddition reactions,[15] rearrangement of epoxides,[16] trans-esterification processes,[17] and synthesis of amino phosphates and quinolines.[18] We wish to report here a remarkable catalytic activity of $InCl_3$ for the [2+3] cycloaddition reaction between organic nitriles and sodium azide under microwave irradiation in DMF (Scheme 1).

Experimental

Melting points were measured by open capillary method and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR -8900 spectrometer. Mass spectra were recorded on LC/MS and EI mode and mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded on a Varian mercury plus-400 spectrometer using TMS as internal standard. All compounds were characterized by melting point, IR, Mass and ^{1}H NMR spectroscopy and identified by comparison in the literature.

General Procedure for Synthesis of 5-substituted 1H- tetrazoles:

In an oven-dried flask sodium azide (0.012 mmol) and $InCl_3$ (10 mol %) were added to a solution of nitrile (0.01 mmol) in dry DMF (1.0 ml). Then, the flask was placed in microwave and irradiated at 70- 90 power (2450 W) for 6- 12 min. (see in Table 2). When TLC analysis showed complete conversion, the reaction mixture was cooled to room temperature and poured in to ice cold water after which it was acidified with 3 N HCl. The resulted crude product was collected by filtration and recrystalized by ethyl acetate and hexane mixture to give desired product in good to excellent yield (70-96 %) under microwave irradiation. Particularly, in some cases for benzylic tetrazoles product does not precipitated after acidification and required extractive work-up by ethyl acetate.

Physical and Spectral Data for the Selected Compounds:-

*5-Phenyltetrazole (**2a**)[10]:*

White solid with 95 % yield; mp = 214-216 ^{o}C (lit. 215-216 ^{o}C); IR (KBr): ν_{max} 3055 (m, C-H), (2980-2460 (brs, N-H), 1608 (s, C=C), 1564 (s, tetrazole), 727-688 (s, mono substituted benzene) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.58-7.62 (m, 3H), 8.02- 8.08 (m, 2H); LC/MS: *m/z* (%) = 147 (100) $[M+H]^+$, 104 (14) $[MH-HN_3]^+$.

*5-(4-Bromophenyl) tetrazole (**2b**)[5]:*

White solid with 81 % yield; mp =266-268 ^{o}C (lit. 268-269 ^{o}C); IR (KBr): ν_{max} 3088 (m, C-H), (2999-2422 (brs, N-H), 1604 (s, C=C), 1483-1431 (s, tetrazole), 829 (s, *p*-disubstituted

benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.8 (d, J = 8.4 Hz, 2H), 7.9 (d, J= 8.4 Hz, 2H); LC/MS: *m/z* (%) = 225 (100) $[M+H]^+$, 182 (17) $[MH-HN_3]^+$.

*5-(4-Chlorophenyl) tetrazole (**2c**)[4]:*

White solid with 94 % yield; mp =252-254 °C (lit. 252-253 °C); IR (KBr): ν_{max} 3068 (m, C-H), (2997-2426 (brs, N-H), 1610 (s, C=C), 1489-1436 (s, tetrazole), 831 (s, *p*-disubstituted benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.7 (d, J = 8.8 Hz, 2H), 8.05 (d, J=8.8 Hz, 2H); MS(EI): *m/z* = 179 $[M-H]^-$, 137 $[M-HN_3]^-$.

*5-(3-Chlorophenyl) tetrazole (**2d**)[5]:*

White solid with 79 % yield; mp =110- 115 °C; (KBr): ν_{max} 3068 (m, C-H), (2968-2430 (brs, N-H), 1558 (s, C=C), 1473 (s, tetrazole), 891 (s, *m*-disubstituted benzene) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 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-(4-Fluorophenyl) tetrazole (**2f**):*

White solid with 78 % yield; mp = 210 °C; IR (KBr): ν_{max} 3074 (m, C-H), (2920-2416 (brs, N-H), 1610 (s, C=C), 1500 (s, tetrazole), 842 (s, *p*-disubstituted benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.47 (t, J = 8.8 Hz, 2H), 8.07-8.11 (m, 2H); LC/MS: *m/z* (%) = 165 (100) $[M+H]^+$,122 (17) $[MH-HN_3]^+$; HRMS calc. for $C_7H_6FN_4$ (M^++ H) 165.0576, found 165.0568.

*5-(4-tolyl) tetrazole (**2g**)[10]:*

White solid with 80 % yield; mp = 248-250 °C (lit. 248-249 °C); IR (KBr): ν_{max} 3062 (m, C-H), 2983-2400 (brs, N-H), 2972 (s, CH_3) 1590 (s, C=C), 1492(s, tetrazole), 823 (s, *p*-disubstituted benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 7.41 (d, J=8.4 Hz, 2H), 7.96 (d, J=8.4 Hz 2H); MS (EI): *m/z* = 159 $[M-H]^-$, 130 $[M-HN_2]^-$.

*5-(3-tolyl) tetrazole (**2h**)[6]:*

White solid with 85 % yield; mp= 150-152 °C; IR (KBr): ν_{max} 3068 (m, C-H), 2983-2426 (brs, N-H), 2910 (s, CH_3) 1560 (s, C=C), 1485 (s, tetrazole), 798 (s, *p*-disubstituted benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.4 (s, 3H), 7.39-7.51 (m, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H); LC/MS: *m/z* (%) = 161 (100) $[M+H]^+$, 118 (18) $[MH-HN_3]^+$.

*5-(2-nitro,4-tolyl) tetrazole (**2i**):*

Yellow solid with 70 % yield; mp= 180- 182 °C; IR (KBr): ν_{max} 3065 (m, C-H), 2980-2432 (brs, N-H), 2955 (s, CH_3), 1603 (s, C=C), 1464 (s, tetrazole), 869 (s, substituted benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.45 (s, 3H), 7.74-7.80 (m, 2H), 8.1 (s, 1H); ^{13}CMR (400 MHz, $CDCl_3$+DMSO-d_6): 19.76, 94.06, 115.96, 130.06, 132.4, 133.64, 141.2, 146.8; LC/MS: *m/z* (%) = 206 (100) $[M+H]^+$, 163 (9) $[MH-HN_3]^+$; HRMS calc. for $C_8H_8N_5O_2$ (M^++ H) 206.0678, found 206.0672.

*5-(4-Methoxyphenyl) tetrazole (**2j**)[10]:*

White solid with 76 % yield; mp= 230-231 °C (lit. 231-232 °C); IR (KBr): ν_{max} 3078 (m, C-H), (2983-2480 (brs, N-H), 1612 (s, C=C), 1500 (s, tetrazole), 1267 (s, aromatic C-O), 1182 (s, methoxy C-O), 835 (s, *p*-disubstituted benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 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 $[M+H]^+$, 134 $[MH-HN_3]^+$.

*5-Benzyltetrazole (**2k**)[20]:*

White solid with 80 % yield; mp= 120-122 °C (lit. 121-122 °C); IR (KBr): ν_{max} 3078 (m, C-H), 2962-2460 (brs, N-H), 1608 (s, C=C), 1542 (s, tetrazole), 698 (s, mono substituted

benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.28 (s, 2H), 7.25-7.27 (m, 3H), 7.31-7.35 (m, 2H); MS (EI): *m/z* = 160 $[M+H]^+$, 91 $[M\text{-}CHN_4]^+$.

*5-((4-methoxyphenyl)methyl) tetrazole (**2l**):*

White solid with 71 % yield; IR (KBr): ν_{max} 3105 (m, C-H), 2966-2484 (brs, N-H), 1610 (s, C=C), 1512 (s, tetrazole),1247 (s, CH_2), 848 (s, *p*-disubstituted benzene) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.19 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.21(s, 2H), 3.75 (s, 3H); LC/MS: *m/z* =191 (100)$[M+H]^+$, 121 (27) $[M\text{-}CHN_4]^+$; HRMS calc. for $C_9H_{11}N_4O$ (M^++ H) 191.0933, found 191.0930.

*5-Benzhydryltetrazole (**2m**)[7]:*

White solid with 96 % yield; mp=164-165 ^oC (lit. 164-165 ^oC); IR (KBr): ν_{max} 3088 (m, C-H), 3003-2455 (brs, N-H), 1599 (s, C=C), 1496 (s, tetrazole), 1246 (s, CH_2), 744 (s, substituted benzene) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.86 (s, 1H), 7.19-7.21 (m, 4H), 7.30-7.36 (m, 6H); LC/MS: *m/z* (%) = 237 (100)$[M+H]^+$, 167 (29) $[M\text{-}CHN_4]^+$.

*3-((2H-tetrazol-5-yl)methyl)-6-methyl-2-p-tolylimidazo[1,2-a]pyridine (**2n**):*

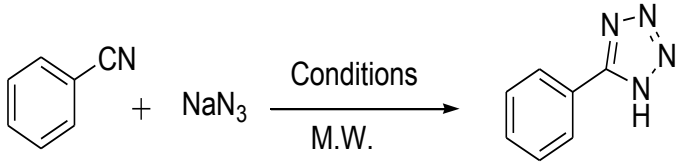
Faint greenish solid with 76 % yield; mp=248-250 ^oC; IR (Nujol): ν_{max} 2920 (m, C-H), 3181 (brs, N-H), 1612 (s, C=C), 1463 (s, tetrazole), 1377 (s, CH_2), 721 (s, substituted benzene) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$and CD_3OD) δ: 2.39 (s, 6H), 4.63 (s, 2H), 7.25-7.28 (d, 2H, *J* = 8.3Hz) 7.42-7.45 (d, 2H, *J* = 9Hz) 7.52-7.57 (m,3H) 8.21 (s, 1H); LC/MS: *m/z* (%) = 305.15 (100)$[M+H]^+$, 277.10 (32). MS (ESI): *m/z* = 305.15 (100)$[M+H]^+$.

*Ethyl 2-(2H-tetrazol-5-yl)acetate (**2o**):*

White solid with 84 % yield; mp=130-132 ^oC; IR (KBr): ν_{max} 3472 (brs, N-H), 1747(s, C=O), 1568 (s, tetrazole) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.20 (t, 3H *J* = 7.0Hz), 4.14 (q, 2H *J* = 7.0Hz), 4.17 (s, 2H); LC/MS: *m/z* (%) = 157 (100)$[M+H]^+$.

Result and Discussion

Initially, the reaction of benzonitrile and sodium azide was selected as a model reaction to optimize the reaction conditions under microwave irradiation and the obtained results are listed in Table 1. When the reaction was carried out in without solvent with different catalyst (20 mol %) (Table 1, entries 1-5), it was found that $InCl_3$ was more effective than other catalysts and a moderate yield (61%) could be obtained (Table 1, entry 5). For improving the yield of this cycloaddition reaction, we verify the reaction with different solvents (Table 1, entries 6-10) and remarkably DMF (Table 1, entry 10) found to be most suitable solvent for this transformation. With these results in hand we investigated catalytic amount required for this transformation and found that 10 mol% of $InCl_3$ (Table 1, entry 13) catalyst gives excellent yield (95 %). The reaction was completed only in few minutes, a reaction time considerably shorter than those previously reported[19] by using $ZnCl_2/H_2O$ under microwave irradiation (6 hrs. with 78 % yield). While, in absence of catalyst reaction does not proceeds forward (Table 1, entry 11) and excess amount of the catalyst did not improve the yield to a greater extent.



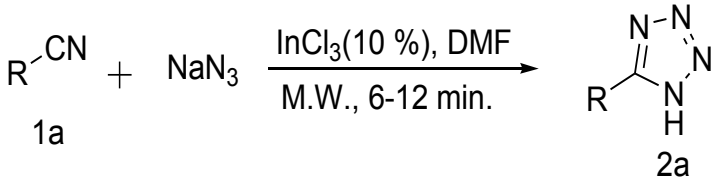
Scheme 1. Synthesis of 5-phenyltetrazole under microwave irradiation.

Table 1. Screening of reaction parameters for the formation 5-phenyltetrazole[a]

Entry	Catalyst (mol %)	Solvent (1 ml)	Time (min.)	Yield[b] (%)
1	MoO_3-SiO_2 (20 mol %)	----	15	NA
2	Alum (20 mol %)	----	10	< 50
3	$ZnCl_2$ (20 mol %)	----	15	< 20
4	ZnO (20 mol %)	----	15	NA
5	$InCl_3$ (20 mol %)	----	10	61
6	$InCl_3$ (20 mol %)	DMSO	10	82
7	$InCl_3$ (20 mol %)	Xylene	10	79
8	$InCl_3$ (20 mol %)	Isopropanol	10	54
9	$InCl_3$ (20 mol %)	PEG-400	10	65
10	$InCl_3$ (20 mol %)	DMF	5	95
11	$InCl_3$ (0 mol %)	DMF	30	NA
12	$InCl_3$ (5 mol %)	DMF	10	78
13	$InCl_3$ (10 mol %)	DMF	5	95

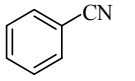
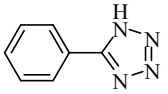
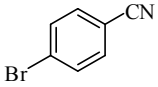
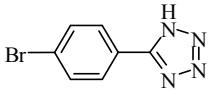
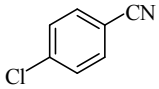
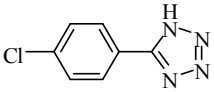
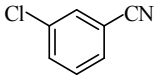
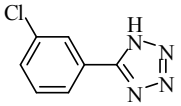
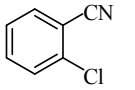
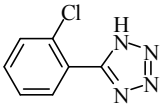
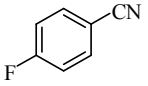
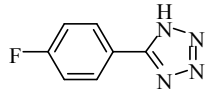
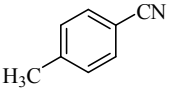
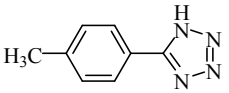
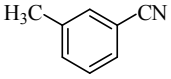
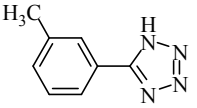
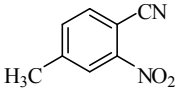
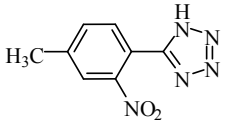
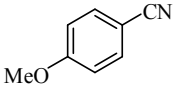
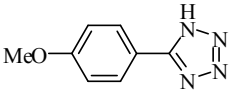
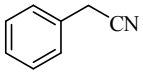
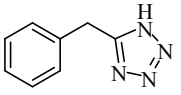
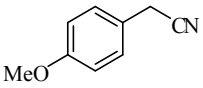
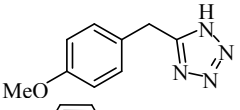
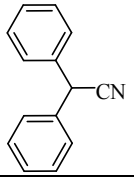
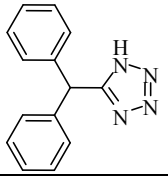
[a] *Reaction condition: Benzonitrile (0.01 mmol), NaN_3 (0.012 mmol), Solvent (1 ml).*
[b] *Isolated product recrystallized by EtOAc: Hexane.*

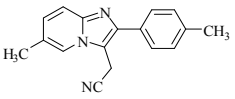
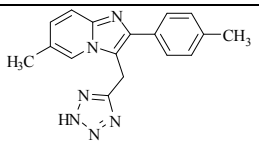
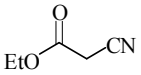
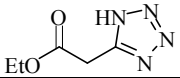
After an optimization study 10 mol % of $InCl_3$ furnished good results, we achieved a higher degree of reproducibility when we used the DMF as a solvent in our studies. The objective of the present research was to examine with a wider range of organic nitriles that contained aliphatic, heterocyclic, benzylic and aromatic with electron-withdrawing and electron-releasing groups to develop a reproducible protocol. Our results are summarized in Table 2, 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 8.0 min. (Table 2, entries 3), while the ortho-derivative rendered only 71% conversion during 11.5 min. (Table 2, entries 5). This pattern was consistently observed with all other substituent's (Table 2, entries 7, 8, 9). The present results also indicate that benzylic nitriles were successfully converted to their tetrazoles (Table 2, entries 11-13) but required extractive work up because of their solubility in water. It is interesting to note that both, activating and



Scheme 2. Synthesis of 5-substituted 1*H*- tetrazole.

Table 2. Synthesis of 5-substituted 1*H*- tetrazole catalysed by $InCl_3$ (10 mol %) under M.W. irradiation[a].

Entry	Nitrile	Time (min.)	Product	Product Code	Yield[b](%)
1a		8.0		2a	95
1b		10.0		2b	81
1c		8.0		2c	94
1d		6.0		2d	79
1e		11.5		2e	71
1f		10.0		2f	78
1g		10.0		2g	80
1h		8.5		2h	85
1i		12.0		2i	70
1j		10.0		2j	76
1k		7.0		2k	80
1l		11.5		2l	71
1m		6.0		2m	95

1n		10.0		2n	76
1o		6.0		2o	84

[a] *Reaction condition: nitrile (0.01 mmol), NaN_3 (0.012 mmol), $InCl_3$ (10 %), DMF (1 ml).*
[b] *Isolated pure product .*

deactivating groups furnished surprisingly good conversions. A modified reaction procedure made the easy isolation and purification of compounds. As indicated in the experimental section, the yields of the compounds made under this investigation under microwave-assisted conditions are consistently higher than those reported under conventional and microwave conditions. No explosion will occurred in the development of this work. The necessary adequate precautions were taken against the eventuality. In all cases products are isolated and characterized by IR, M.P., ^{1}H NMR and Mass spectroscopy.

Conclusion

In conclusion, we have developed a highly reproducible protocol for the preparation of 5-substituted 1*H*-tetrazole from variety of organic nitriles. The use of $InCl_3$ (10 mol %) under microwave irradiation allows the easy preparation of 5-substituted 1*H*-tetrazole in good to excellent yield. This method has the advantages of higher yields, milder reaction conditions, shorter reaction time and convenient procedure.

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References

1. (a) Zubarev V Yu, Ostrovskii V A, *Khim. Geterotsikl. Soedin*.; 2002, 867. (b) Herr R J, *Bioorg. Med. Chem. Lett*., 2002, **10**, 3379; (c) Koldobskii G I, Kharbash R V, *Zh. Org. Khim.*, 2003, **39**, 489.
2. Katritzky A R, Rees C W, *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984.
3. Ostrovskii V A, Koldobskii G I*., Ros. Khim. Zh*., 1997, **41(2)**, 84.
4. John E O, Kirchmeier R L, Shreeve J M, *Inorg.chem*., 1989, **28**, 4629.
5. Huisgen R, Sauer J, Sturm H J, Markgraf J H, Chem. Ber., 1960, **93**, 2106.
6. Wittenberger S J, *Org. Prep. Proc. Int.* 1994, **26**,499.
7. Amantini D, Beleggia R, Fringuelli F, Pizzo F, Vaccoro L, *J. Org. Chem.,* 2004, **69**, 2896.
8. Grzonka Z, Liberek B, *Roczniki Chemii* 1971, **45**, 967.
9. (a) Dunica J V, Pierce M E, Santella J B, *J. Org. Chem,*. 1991, **56**, 2395; (b) Wittenberger S J, Donner B G, *J. Org. Chem.,* 1993, **58**, 4139.
10. Demko Z P, Sharpless K B, *J. Org. Chem*., 2001, **66**, 7945.
11. (a)Nandre K P, Patil V S, Bhosale S V, *Chinese Chemical Letters*, 2011, **7**, 777; (b) Gutmann B, Roduit J P, Roberge D, Kappe C O, *Angew. Chem. Int. Ed.* 2010, **49***,* 7101.
12. Katritzky A R, Singh S K, *J. Org. Chem.*, 2002, **67**, 9077.

13. Babu S A, Yasuda M, Baba A, *Org. Lett.*, 2007, **9**, 405.
14. Reddy B G, Kumareswaran R, Vankar Y D, *Tetrahedron Lett.* 2000, **41 (52)**, 10333.
15. Yadav J S, Reddy B V S, Kondaji G, *Synthesis*, 2003, **7**, 1100.
16. Ranu B C, Jana U, *J. Org. Chem.,* 1998, **63**, 8212.
17. Ranu B C, Dutta P, Sarkar A, *J. Org. Chem.,* 1998, **63**, 6027.
18. Ranu B C, Hajra A, Jana U, *Tetrahedron Lett.,* 2000, **41**, 531
19. Myznikov L V, Roh J, Artamonova T V, Hrabalek A, Koldobskii G I, *Russian Journal of Organic Chemistry*, 2007, **43(5)**,765.
20. Das B, Reddy C R, Kumar D N, Krishnainah M, Narender R, *Synlett*, 2010, **31**, 0391.