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An Improved One-pot Method for the Synthesis of 1,5-Disubstituted Tetrazoles from Secondary amides using Titanium Tetrachloride ($TiCl_4$)

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ABSTRACT

A novel protocol for the synthesis of 1,5-disubstituted tetrazoles from secondary amides has been developed using $TiCl_4$ as a catalyst for first time. In the present protocol, the use of $TiCl_4$ enhances the reactivity of sodium azide towards secondary amides. This methodology may be used efficiently for the synthesis of variety of 1,5-disubstituted tetrazoles.

Keywords: 1,5-disubstituted tetrazole, $TiCl_4$, NaN_3.

Recently, the tetrazole ring has attracted considerable attention, especially in medicinal chemistry, due to its isosteric nature with carboxyl group. The 1,5-disubstituted tetrazoles were incorporated into longer peptides as isosteres for the cis-amide bond.[1] These substituents have displayed similar types of biological activities because of their physicochemical properties, though they are structurally different. The replacement of the cis-amide group by 1,5-disubstituted tetrazole enhances the metabolic stability of the molecule. The 1,5-disubstituted tetrazole moieties are found in numerous biologically active substances. Some of these scaffolds exhibit various types of biological properties,

such as antiviral,[2] anti-inflammatory,[3] anti-plasmodial,[4] antitubercular,[5] anti-HIV,[6] antibacterial,[7] antifungal,[8] anticonvulsant,[9], antinociceptive [10] etc.

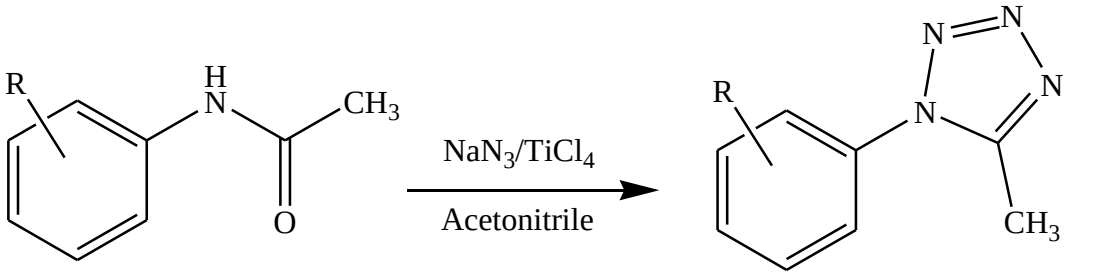
The synthesis of 1,5-disubstituted tetrazole is well described in literature, where it can be synthesized from amides,[11] thioamides,[12] imidoyl chlorides,[13] imidoyl benzotriazoles,[14] oximes,[15] isocyanates,[16] etc. Out of these, the secondary amides are easily available or can be easily prepared from amines, so the interest has been created towards the use of amides in the synthesis of 1,5-disubstituted tetrazoles. The several methods have been reported for the conversion of secondary amide to the corresponding 1,5-disubstituted tetrazole. George S. *et al*[5] have reported the synthesis of 1,5-disubstituted tetrazole using PCl_5 followed by NaN_3 where formation of imidoyl chloride as an intermediate take place. Further Katritzky A. R. *et al*[14] have reported the synthesis of 1,5-disubstituted tetrazole, with the formation of imidoylbenzotriazole as an intermediate. *Schroeder et al*[17] have reported the preparation of 1,5-disubstituted tetrazole from secondary amide using NaN_3, triphenyl phosphine and diethyl azodicarboxylate. Recently, *Najafi P.* et al[18] showed that tetrachlorosilane-sodium azide system leads to the formation of 1,5-disubstituted tetrazole from the secondary amide. However, many of these reported methods suffer from either long reaction time or tedious work up and low yields. Therefore, we have tried for a more efficient method for the preparation of 1,5-disubstituted tetrazoles. We report here a simple and facile one pot cycloaddition reaction for the synthesis of 1,5-disubstituted tetrazole from secondary amide using NaN_3 in presence of Titanium tetrachloride ($TiCl_4$) as a catalyst.

Experimental.

All the secondary amides were synthesized in our laboratory where as other chemicals were purchased from commercial suppliers. Melting points were determined in open capillaries and were uncorrected. The progress of reaction and purity of the product were monitored by thin layer chromatography using precoated Silica 60/UV_{254} (SDFCL). NMR spectra were recorded using a Bruker DRX-300 (300MHz) spectrometer and are reported in δppm downfield from TMS as internal standard. FT-IR spectra were recorded on Shimadzu IRAffinity-1S spectrophotometer and are reported in cm^{-1}.

Result and Discussion.

Herein, we found for the first time that, the titanium tetrachloride acts very efficiently as a catalyst for one-pot conversion of secondary amides into 1,5-disubstituted tetrazoles using sodium azide in acetonitrile. It has been found that the secondary amides react with NaN_3 in presence of $TiCl_4$ in acetonitrile on heating for 6-8 hrs. to give 1,5-disubstituted tetrazoles in good yields (85-95%). The reaction time was found to be lesser as compared with other reported methods. The secondary amides having substitution at *para*- position gives high yield and show less reaction time when compared with *meta*- and *ortho*- phenyl substituted secondary amides. The obtained products were characterized by IR and NMR spectral data. The melting points were compared with the literature data.



N-phenylacetamide

5-methyl-1-phenyl-1*H*-tetrazole

Scheme-1. Synthesis of disubstituted tetrazoles (1-7)

General Procedure for the preparation of 1,5-disubstituted tetrazole (1).

To a stirred solution of acetanilide (2gm, 0.5moles) in dry acetonitrile (5ml) at 0-5^{0}C, $TiCl_4$ (2.8gm, 1.0moles) was added drop wise with stirring and the mixture was stirred at room temperature for 30 min. Then Sodium azide (0.93gm, 0.5 mol.) was added to it and the reaction mixture was heated at 80-90^{0}C. After 2 hrs remaining amount of sodium azide (0.93gm, 0.5 mol.) was added to reaction mixture and heating was continued for 4-6 hrs. The reaction was monitored by TLC after 3hrs. Then the reaction mixture was cooled and poured over crushed ice and the product separated out was filtered, washed with water, dried and recrystallized from alcohol.

5-Methyl-1-phenyl-*1H*-tetrazole (1). White crystals; yield 87 %; mp. 103 ^{0}C; ^{1}H-NMR ($CDCl_3$): δ 7.48 (s, 5H), 2.38 (s, 3H); FT-IR: 3061, 2947, 1593, 1498, 1458, 1411, 1377, 1290, 1170, 1116, 1080, 985, 923, 850, 765, 690 cm^{-1}.

5-methyl-1-m-tolyl-1*H*-tetrazole (2). White crystals; yield 87 %; mp. 87 ^{0}C; ^{1}H-NMR ($CDCl_3$): δ 7.34 (m, 4H), 2.41 (s, 3H); 2.28(s, 3H); FT-IR: 3051, 2931, 2864, 1631, 1585, 1518, 1496, 1462, 1410, 1383, 1292, 1269, 1118, 1082, 1028, 987, 800, 767, 721 cm^{-1};

5-methyl-1-(4-nitrophenyl)-1*H*-tetrazole (3). Light yellow crystals; yield 87 %; mp. 216 ^{0}C; ^{1}H-NMR ($CDCl_3$): δ 8.17 (dd, 2H), 8.24 (dd, 2H); 3.89(s, 3H); FT-IR: 3097, 3078, 2941, 2870, 1610, 1587, 1527, 1485, 1410, 1346, 1288, 1116, 1095, 995, 912, 871, 813, 746 cm^{-1}.

5-methyl-1-(3-nitrophenyl)-1*H*-tetrazole (4). Light yellow crystals; yield 87 %; mp. 152 ^{0}C; ^{1}H-NMR ($CDCl_3$): δ 8.48 (m, 1H), 8.40 (m, 1H); 8.11 (m, 1H), 7.80 (m, 1H); 2.49(s, 3H); FT-IR: 3080, 2997, 1614, 1583, 1527, 1496, 1435, 1354, 1298, 1109, 1080, 1030, 910, 842, 806, 752 cm^{-1}.

5-methyl-1-(2-nitrophenyl)-1*H*-tetrazole (5). Light yellow crystals; yield 87 %; mp. 118 ^{0}C; ^{1}H-NMR ($CDCl_3$): δ 8.41 (m, 1H), 8.22 (m, 1H); 7.92 (m, 1H), 7.75 (m, 1H); 2.15(s, 3H); FT-IR: 3093, 2989, 1608, 1581, 1527, 1496, 1411, 1344, 1305, 1280, 1257, 1112, 1089, 1024, 987, 854, 750, 723 cm^{-1}.

5-methyl-1-(4-fluorophenyl)-1*H*-tetrazole (2). White crystals; yield 87 %; mp. 82 ^{0}C; ^{1}H-NMR ($CDCl_3$): δ 7.65 (dd, 2H), 7.39 (dd, 2H); 2.42(s, 3H); FT-IR (KBr): 3120, 2983, 1600, 1514, 1411, 1383, 1274, 1230, 1157, 1093, 1041, 989, 839, 690, 613 cm^{-1}.

1-(4-bromophenyl)-5-methyl-1*H*-tetrazole (2). White crystals; yield 87 %; mp. 118 ^{0}C; ^{1}H-NMR ($CDCl_3$): δ 7.75 (dd, 2H), 7.58 (dd, 2H); 2.45(s, 3H); FT-IR: 3084, 2983, 2879, 1516, 1492, 1408, 1273, 1118, 1101, 1076, 1039, 1008, 844, 821 cm^{-1}.

Conclusion.

In conclusion, we have developed a novel protocol for high yielding method for the synthesis of 1,5-disubstituted tetrazoles from secondary amides using $TiCl_4$ as a catalyst for first time. The use of $TiCl_4$ enhances the reactivity of inexpensive sodium azide towards

secondary amides. This methodology may be used efficiently for the synthesis of variety of 1,5-disubstituted tetrazoles.

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