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A novel approach for the synthesis of 5-substituted tetrazole derivatives from primary amides in mild one-step method.

Abdel-Aziz S. El-Ahl, Saad S. Elmorsy*, Akram H. Elbeheery and Fathy A. Amer.

Chemistry Department, Faculty of Science, Mansoura University, Mansoura - EGYPT

Abstract: **A new mild one-step method for the conversion of primary acid amides to 5-substituted tetrazoles in nearly quantitative yields employing triazidochlorosilane (TACS) is reported.**

The class of tetrazole compounds have been used both as anticancer[1] and antimicrobial[2] agents. Recently, they have received increased attention due to their potential biological activity and industrial applications[3-5].

The use of triazidochlorosilane (TACS) as azide transfer reagent has spurred both the search for the conversion of aldehydes to nitriles or acid azides, while ketones are converted with rearrangement into their corresponding tetrazoles[6-8] and the development of general synthetic approaches for chemoselective formation of tetrazole derivatives. We are reporting herein the first direct one-pot conversion of primary amides into 5-substituted tetrazoles. Thus, acid amides on treatment with triazidochlorosilane (TACS) in acetonitrile under reflux yielded 5-aryltetrazole derivatives in nearly high yields as shown in Table 1 (eq. 1).

(7) (8) ...eq. 1

Table (1): Reaction of triazidochlorosilane (TACS) with primary amides

Entry no.	Substrate	Time hr.	Product[9]	Yield %
1	Benzamide	2	5-Phenyl-1H-tetrazole[10] **(1)**	92
2	4-Chlorobenzamide	1.5	5-(4-Chlorophenyl)-1H-tetrazole **(2)**	94
3	2-Chlorobenzamide	1.5	5-(2-Chlorophenyl) -1H-tetrazole **(3)**	90
4	4-Methylbenzamide	2	5-(4-Methylphenyl) -1H-tetrazole[11] **(4)**	91
5	4-Methoxybenzamide	2	5-(4-Methoxyphenyl)-1H-tetrazole **(5)**	88
6	4-Nitrobenzamide	2.5	5-(4-Nitrophenyl)-1H-tetrazole **(6)**	76
7	1,1'-Biphenyl-4-carboxamide **(7)**	2.5	5-(4'-1,1'-Biphenyl)-1H-tetrazole **(8)**	89
8	Phenoxyacetamide **(9)**	2	5-(Phenoxymethyl)-1H-tetrazole[12] **(10)**	83

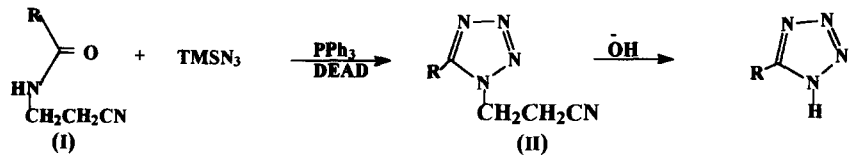
The reaction of triazidochlorosilane (TACS) is general and reproducible for both aromatic and aliphatic amides. Phenoxyacetamide (9) reacts at the same conditions (entry 8) to produce 5-phenoxymethyltetrazole [12] (10) (eq. 2).

(9) (10)

This tetrazole formation tolerated a variety of functional groups on the aromatic ring. Thus chloro-, methyl-, methoxy-, and nitro- containing aryl amides underwent the reaction in very good to excellent yields. Some reactants in somewhat lower yields, and slowly, because the reactions of electron-poor aryl amide (entry 6) are slow relative to electron rich aryl amide (entries 2, 3, 4, 5).

The ultraviolet absorption spectra of the products were in agreement with literature for 5-aryl tetrazole [13,14]. The interaction of the phenyl group with the tetrazole ring produces a new chromophore that shows a single absorption band [15]. Introduction of chlorine at the para-position of 5-phenyltetrazoles produces a shift of the band to longer wavelength and an increase in the extension coefficient (ε). With chlorine in the ortho-position the band shifted to shorter wavelength maximum. The hypsochromic shift caused by halogens in the ortho-position may be due to steric effect of the ortho-substituted which makes attainment of coplanarity of the two ring systems difficult and disturbs the resonance interaction of the phenyl and tetrazoles rings.

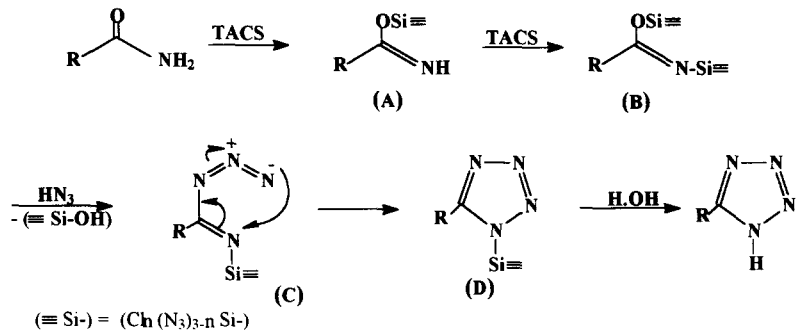
Amides were reported to be unreactive towards hydrazoic acid or sodium azide [16] but if the protected primary amides are first allowed to react with phosphorus pentachloride, the formed imidoyl chloride reacts with hydrazoic acid to form a tetrazole from the iminoyl azide as intermediate. Treatment of primary amides with PCl_5 produced the corresponding nitriles [17]. Azidotrimethylsilane [18] was used to produce the tetrazole derivative (II) from the corresponding cyanoethyl protected amide (I) in presence of triphenylphosiphine (PPh_3), diethylazodicarboxylate (DEAD). Thus, cyanoethyl group has been used as a protecting group to facilitate the formation of tetrazole without the conversion of the primary amide back to its corresponding nitrile. The cyanoethyl tetrazole (II) deprotected to form the 5-substituted tetrazole by using aqueous base as shown in Scheme 1.



(I) (II)

Scheme 1

Benzonitrile was not detected in the reaction of TACS with acid amide at all. We believe that the formation of tetrazole derivative follows the mechanism depicted in scheme (2). In conclusion, three types of effects of a triazidochlorosilane reagent in the reaction, (i) an formation of iminoylsilyl ether [A] from amide, (ii) a greater tendency of it to protect the intermediate (A) to prevent the formation of nitrile and the intermediate (B) is predominant, (iii) the formation of imidoyl azide (C) which cyclized directly into the tetrazole (D). Further, as described in the scheme 2, a preference between the effect (ii) and nitrile formation is critically dependent on the nature of triazidochlorosilane (TACS) which provides a very good protecting species easily departure in aqueous workup.



Scheme 2

In a typical procedure for reaction of TACS with amides, a mixture of tetrachlorosilane (5 mmol), sodium azide (15 mmol) in dry acetonitrile (10 ml) and 4-chlorobenzamide (5 mmol) was refluxed and stirred with exclusion of moisture. The reaction mixture was poured into ice-cooled sodium carbonate solution and extracted with chloroform (3x20 ml). The solvent was distilled off under reduced pressure and the residue was crystallized from ethanol to give 5-(4-chlorophenyl)-1H-tetrazole (2), m.p. = 262 °C (Lit. [14] m.p. = 262-263 °C).

The chemistry reported above permits the direct formation of tetrazole from primary amides. The reaction proceeds under mild conditions and in very good to excellent yields without catalyst. It is regioselective for preparing 5-substituted tetrazole. The method outlined will be of high interest, not only for the compounds containing tetrazole group which is increasingly becoming more important as a carboxylic acid isostere [19], but for the introduction of triazidochlorosilane (TACS), generated in situ, as a versatile synthetic reagent.

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9. The structure of isolated products were fully characterized using elemental analysis, IR, UV, ^{1}H-NMR and mass spectra.
10. The mass spectra of compound 1 showed the M^+ at 146 and the base peak at 118 obtained by loss of nitrogen (N_2).
11. ^{1}H-NMR ($CDCl_3$) of compound 4 revealed a doublet at δ = 7.75-7.71 (2H, J = 8 Hz, ArH), a doublet at δ = 7.10-7.06 (2H, J = 8 Hz, ArH), and a singlet at δ = 2.18 (3H, CH_3).
12. ^{1}H-NMR ($CDCl_3$) of compound 10 revealed a multiplet at δ = 7.37-7.26 (2H, m-ArH), a multiplet at δ = 7.03-6.91 (3H, o, p-ArH) and a singlet at δ = 5.47 (2H, -OCH_2-).
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15. UV data for compounds (1-6) and (8)

Compd. no.	1	2	3	4	5	6	8
max(nm) (ε)	241 (15,900)	247 (20,400)	234 (9,600)	246 (16,700)	259 (16,900)	278 (14,700)	250 (17,300)

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