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SYNTHESIS OF 1,2,3-TRIAZOLES

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Abstract – 4-Phenyl-1-(*p*-toluenesulfonamido)-1,2,3-triazole (**1**) is obtained when phenacyl halides react with tosyl hydrazide in one-pot process.

INTRODUCTION

The most common method for the synthesis of 1,2,3-triazoles is the cycloaddition of an alkyne to an azide,[1] however a further disadvantage is the lack of regiospecificity. On the other hand, it has been published the obtention of 1,2,3-triazoles[2] by cyclization of α,α-dichloroketone tosylhydrazones or the preparation of 1-substituted 1,2,3-triazoles by the reaction of dichloroacetaldehyde tosyl- or mesitylhydrazone with ammonia, amino derivatives and hydrazine.[3]

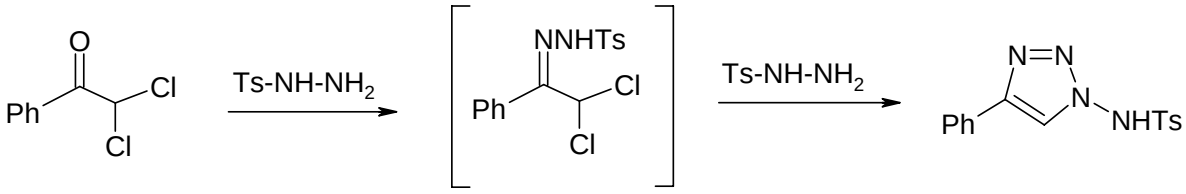
1,2,3-Triazoles are of an importance in organic synthesis, medicinal chemistry and industry. For instance, antileukemic and antitumor *in vitro* activities have been evaluated.[4] Some of them show selective activity *in vitro* against *Escherichia coli*,[5] and muscarinic,[6] antibacterial[7-9] or β-lactamase inhibitory activity.[10] 1,2,3-Triazole derivatives are also used as a potent androgen synthesis inhibitor in mice.[11] In agrochemicals, 1,2,3-triazole derivatives show pesticidal, fungicidal,[12] insecticidal and acaricidal activity.[13] Some benzotriazoles are resistant to heat and are useful antireflective absorbing agents.[14] Anticorrosives containing tolyltriazol have been developed for aluminium.[15]

RESULTS AND DISCUSSION

In the literature it is mentioned[2] that when α,α-dichloroacetophenone was treated with tosyl hydrazide the isolated compound was unexpectedly cyclized to 4-phenyl-1-(*p*-toluenesulfonamido)-1,2,3-triazole (**1**) in 20% yield, as showed in Scheme 1.

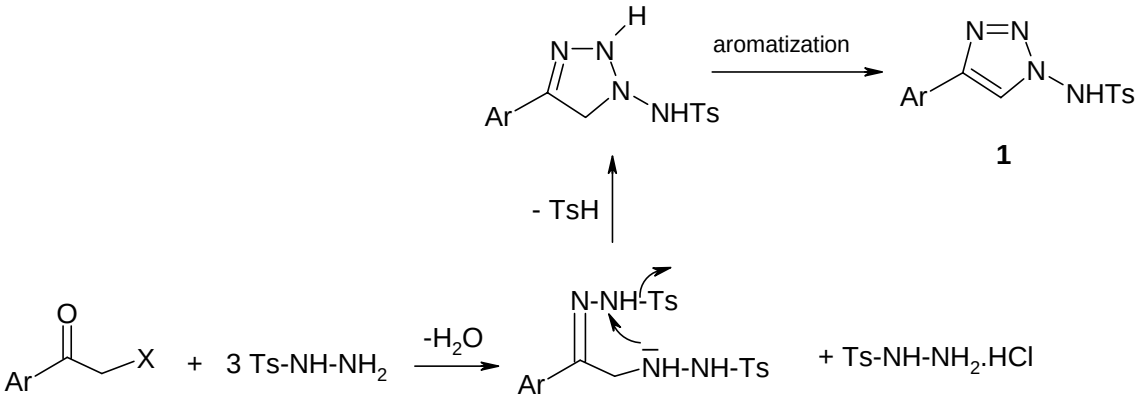
In our study we have obtained a series of triazoles in moderate yields (33-55%) using α-monohalogenated acetophenones as starting material.

The process takes place through the formation of the corresponding tosylhydrazone with subsequent nucleophilic substitution of the chloro atom by another tosyl hydrazide molecule. Further intramolecular



Scheme 1

attack of nitrogen electron pair on the amidic nitrogen of hydrazone results in nucleophilic substitution of tosyl group at N-atom (substitution of a tosyl group by ammonia in tosylhydrazone is known[3]). Subsequent aromatization takes place with the formation of 1,2,3-triazole (**1**) as indicated in Scheme 2.



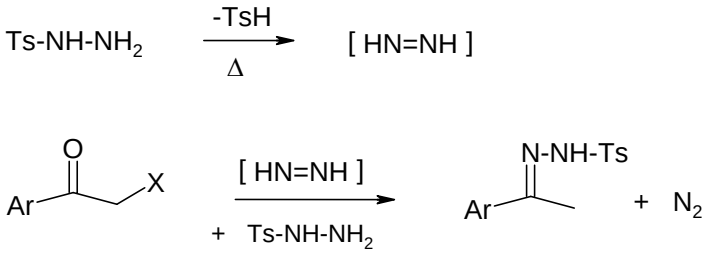
X= Cl, Br
Ar= C_6H_5, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Ph-C_6H_4

Scheme 2

As it is indicated in the *General Procedure*, the reaction is carried out under refluxed conditions (at room temperature the formation of the hydrazone is more difficult). However, it is well known the thermal unstability of the sulfonyl hydrazides which decompose to form "*in situ*" diimide[16] which itself is a good reducing agent. In our case, phenacyl halide was added dropwise into a tosyl hydrazide methanol solution. The reduction potential of phenacyl halides is low (near –0.6V vs SCE).[17] Thus under our experimental conditions the reduction of these substrates takes place leading to a large amount of the corresponding acetophenone tosylhydrazone, according to Scheme 3. To avoid this undesirable reaction the process was run at –3ºC but, in this case no traces of **1** were found.

To summarize, the only two products formed from phenacyl halides are the 1,2,3-triazol and the acetophenone tosylhydrazone.

It has also been observed that on refluxing *p*-nitrophenacyl or *p*-phenylphenacyl halides with tosyl hydrazide for 48 h, the tosyl group in the obtained triazole is eliminated and 1-amino-1,2,3-triazoles are afforded.



Scheme 3

In conclusion, the herein described procedure has the advantage to provide better yields of 1,2,3-triazoles as compared to previously reported reactions, without employment of polyhalogenated substrates.

EXPERIMENTAL

MS spectra (EI, ionizing voltage 70ev) were determined with a Hewlett-Packard Model 5988A mass-selective detector equipped with a Hewlett-Packard MS Chem Station. IR spectra were obtained, as dispersions in KBr, on a Perkin-Elmer Model 583 spectrophotometer. ^{1}H NMR and ^{13}C NMR (300MHz & 75.4 MHz respectively) spectra were recorded on a Varian Unity 300 apparatus with deuteriochloroform and deuterated dimethyl sulfoxide as an internal standard. The chemical shifts are given in ppm.

Melting points were determined on a Reichert Thermovar microhot stage apparatus, and are uncorrected. Elemental analyses were performed on a Perkin- Elmer Model 240-B analyzer. The products were purified by silica gel 60 (35-70 mesh) .

GENERAL PROCEDURE

A solution of the corresponding phenacyl bromide (5 mmol in 20 mL of MeOH) was added by dropping to a stirred solution of tosyl hydrazide (15 mmol in 30 mL of MeOH) under refluxed conditions. When the bromide was consumed (after 2-3 h of refluxing) the solvent was removed under reduced pressure. The residue was treated with ether/water and the organic phase dried over Na_2SO_4 and concentrated by evaporation. The resulting solid or oil was chromatographed on a silica gel (21× 3 cm) column, using chloroform:hexane (1/1) or EtOAc:hexane (1/4) as eluent. Spectroscopical description of the obtained 1,2,3-triazols (**1a-f**) is given below.

4-Phenyl-1-(*p*-toluenesulfonamido)-1,2,3-triazole (1a): (42% yield). mp 200ºC (EtOH) [lit.,[9] 201 ºC]. IR(KBr) ν (cm^{-1}) = 3064, 2829, 1594, 1480, 1368, 1170, 965, 812, 764, 691, 670. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.41(s, 3H), 7.39(d, 2H, J=8.2 Hz), 7.46-7.56(m, 3H), 7.60(d, 2H, J=8.2 Hz), 7.71-7.78(m, 2H), 8.10(s, 1H), 12.60(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 21.8, 118.9, 125.8, 128.5, 128.6, 129.4, 130.2, 130.4, 132.3, 135.6, 138.0, 145.2. MS m/z (relative intensity) EI: 314(M^{+}, 5), 159(26), 155(16), 139(17), 131(60), 103(47), 102(55), 91(83), 77(100), 65(33), 51(20).

4-(4-Methoxyphenyl)-1-(*p*-toluenesulfonamido)-1,2,3-triazole (1b): (55% yield). mp 183-184ºC (EtOH). IR(KBr) ν (cm^{-1}) = 3048, 2964, 2838, 1614, 1496, 1359, 1298, 1255, 1171, 1019, 842, 829, 688. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.40(s, 3H), 3.90(s, 3H), 7.14(d, 2H, J=8.7 Hz), 7.46(d, 2H, J=8.2 Hz), 7.68(d, 2H, J=8.2 Hz), 7.77(d, 2H, J=8.7 Hz), 8.08(s, 1H), 12.6(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 21.9, 56.1, 115.9, 118.1, 128.6, 130.1, 130.4, 131.6, 135.8, 138.0, 145.2, 160.8. MS m/z (relative intensity) EI: 344(M^+, 8), 189(43), 161(75), 146(100), 132(59), 117(26), 89(54), 65(28), 51(10). Anal. Calcd for C_{16} H_{16} N_4 O_3 S: C, 55.81; H, 4.65. Found: C, 56.07; H, 4.52.

4-(4-Methylphenyl)-1-(*p*-toluenesulfonamido)-1,2,3-triazole (1c): (38% yield). mp 189ºC (EtOH). IR(KBr) ν (cm^{-1}) = 3051, 2817, 1595, 1494, 1362, 1170, 1086, 965, 814, 688. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.36(s, 3H), 2.41(s, 3H), 7.3(d, 2H, J=8.0 Hz), 7.38(d, 2H, J=8.0 Hz), 7.60(t, 4H, J=8.9 Hz), 8.03(s, 1H), 12.50(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 21.7, 22.0, 123.1, 128.5, 128.6, 130.1, 130.4, 132.0, 135.9, 138.0, 140.0, 145.1. MS m/z (relative intensity) EI: 328(M^+, 6), 173(22), 155(10), 145(53), 130(30), 116(33), 115(100), 103(8), 91(99), 65(40), 51(11). Anal. Calcd for C_{16} H_{16} N_4 O_2 S: C, 58.54; H, 4.88. Found: C, 58.81; H, 4.78.

4-(4-Chlorophenyl)-1-(*p*-toluenesulfonamido)-1,2,3-triazole (1d): (40% yield). mp 178-179ºC (EtOH). IR(KBr) ν (cm^{-1}) = 3079, 2825, 1595, 1481, 1363, 1171, 1097, 965, 825, 682. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.40(s, 3H), 7.35(d, 2H, J=7.7 Hz), 7.56(d, 4H, J=8.7 Hz), 7.73(dd, 2H, J_1=8.7 Hz, J_2=1.8 Hz), 8.12(s, 1H), 12.60(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 21.9, 124.7, 128.5, 129.6, 130.3, 130.4, 132.6, 135.1, 135.4, 136.9, 145.4. MS m/z (relative intensity) EI: 350(M^++2, 1), 348(M^+, 3), 195(5), 193(15), 167(9), 165(27), 155(36), 139(26), 138(10), 136(21), 111(6), 91(100), 65(46), 51(15). Anal. Calcd for C_{15} H_{13} N_4 O_2 Cl S: C, 51.65; H, 3.73. Found: C, 51.92; H, 3.78.

4-(4-Fluorophenyl)-1-(*p*-toluenesulfonamido)-1,2,3-triazole (1e): (33% yield). mp 178-179ºC (EtOH). IR(KBr) ν (cm^{-1}) = 3069, 2924, 2743, 1613, 1595, 1493, 1363, 1170, 1085, 975, 808, 706. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.40(s, 3H), 7.30-7.42(m, 4H), 7.58(d, 2H, J=8.2 Hz), 7.72-7.82(m, 2H), 8.08(s, 1H), 12.60(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 21.7, 116.4, 116.7, 122.4, 128.5, 130.1, 130.4, 130.9, 131.1, 132.3 135.5, 137.1, 145.3, 161.7, 165. MS m/z (relative intensity) EI: 332(M^+, 10), 177(39), 155(23), 149(62), 139(17), 134(23), 121(29), 120(66), 101(100), 91(89), 65(44), 51(11). Anal. Calcd for C_{15} H_{13} N_4 O_2 F S: C, 54.22; H, 3.92. Found: C, 53.98; H, 4.05.

4-(4-Phenylphenyl)-1-(*p*-toluenesulfonamido)-1,2,3-triazole (1f): (35% yield). mp 209-210ºC (EtOH). IR(KBr) ν (cm^{-1}) = 3159, 2854, 1596, 1472, 1415, 1345, 1303, 1163, 1005, 975, 840, 763, 725, 685. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.38(s, 3H), 7.34-7.42(m, 3H), 7.48(t, 2H, J=7.4 Hz), 7.58-7.80(m, 6H), 7.96(d, 2H, J=7.8 Hz), 8.30(s, 1H), 12.60(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 20.5, 125.0, 125.5, 125.9, 126.5, 127.0, 127.2, 128.4, 128.6, 128.8, 130.3, 134.8, 138.9, 142.8. MS m/z (relative intensity) EI:

390(M^+, 1), 221(95), 192(29), 178(50), 165(100), 152(33), 139(30), 115(19), 91(53), 63(33), 51(21). Anal. Calcd for C_{21} H_{18} N_4 O_2 S: C, 64.62; H, 4.62. Found: C, 64.90; H, 4.51.

4-(4-Phenylphenyl)-1*H*-1,2,3-triazole (2f): (40% yield). mp 180-181ºC (EtOH). IR(KBr) ν (cm^{-1}) = 3158, 1635, 1472, 1414, 1345, 1135, 1084, 1005, 974, 872, 840, 763, 725, 685. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.38(t, 1H, J=7.3 Hz), 7.48(t, 2H, J=7.3 Hz), 7.66-7.78(m, 4H), 7.95(d, 2H, J=7.9 Hz), 8.29(s, 1H), 12.20(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 126.9, 127.3, 127.8, 128.3, 129.7, 131.7, 140.4. MS m/z (relative intensity) EI: 222(M^++1, 17), 221(M^+, 100), 192(16), 179(6), 178(6), 165(83), 152(12), 76(9), 63(16), 51(12). Anal. Calcd for C_{14} H_{11} N_3: C, 76.02; H, 4.98. Found: C, 75.85; H, 4.88.

4-(4-Nitrophenyl)-1*H*-1,2,3-triazole (2g): (48% yield). mp 191-193ºC (EtOH). IR(KBr) ν (cm^{-1}) = 3129, 1607, 1513, 1356, 1337, 1234, 1108, 975, 854, 756, 711. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.0(d, 2H, J=8.8 Hz), 8.07(s, 1H), 8.31(d, 2H, J=8.8 Hz), 12.00(br s, NH). ^{13}C NMR (75.4 MHz, DMSO-d_6) δ: 124.5, 126.7, 130.0, 136.8, 145.2, 147.7. MS m/z (relative intensity) EI: 190(M^+, 98),160(59), 144(11), 132(38), 116(4), 89(100), 76(14), 63(42). Anal. Calcd for C_8 H_6 N_4 O_2: C, 50.53; H, 3.16. Found: C, 50.43; H, 3.28.

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