ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2012, *57*(12), 1037-1040

SYNTHESIS OF SOME 1,2,3-TRIAZOLES DERIVATIVES

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Received September 5, 2012

Dimethyl acetylenedicarboxylate (DMAD) undergoes efficient Huisgen 1,3-dipolar cycloaddition reaction with various X-substituted aryl azides (X = 2Cl, 3Cl, $2COOCH_3$, $4COOCH_3$), applying two different conditions, under conventional stirring at room temperature or under microwave irradiation, to afford the corresponding 1,4,5-trisubstituted 1,2,3-triazole **6-9** in good to excellent yields, especially when the phenyl ring of the azide is substituted at the *ortho* position.

INTRODUCTION

There has been widespread interest in 1,2,3-triazoles compounds since they have been widely used in the pharmaceutical materials, science, industries and polymer chemistry.[1-3] The well known protocol to establish the 1,2,3-triazoles ring is the useful and extensively applicable Huisgen reaction between an azide and an alkyn.[4] This reaction owns its usefulness to the relative ease with which both functions can be introduced into various molecules.[5] However this method suffers from some disadvantages: sometimes it requires high reaction temperature which may lead to a decomposition of labile products, a poor regioselectivity and low yields.[6]

The strong need for fast organic reactions has led to a considerable attention in the area of microwave-assisted organic synthesis,[7] one of the most microwave-assisted organic reaction explored is the 1,3-dipolar cycloaddition,[8] the effectiveness of this method in promoting the cycloaddition has been demonstrated.[9-10]

In order to improve the utility of 1,3-dipolar cycloaddition process, we first used a symmetrical alkyne to circumvent the regioselectivity issue, to enhance reaction yields and to reduce the reaction times. We took advantage of microwave irradiations, because microwave synthesis has emerged as a powerful technique to promote a variety of chemical reactions.[11-15] Palacios *et al.* reported that microwave synthesis of 1,2,3-triazoles shows a substantial decrease in reaction times down to 5-30 min as compared to 30-40 h refluxing under thermal conditions for the 1,3-dipolar cycloaddition between phosphonate azides and acetylenic esters.[16] Katritzky *et al.* showed that reaction of organic azides with acetylenic amides was significant only after 12h refluxing in toluene. As a contrast, microwave dielectric heating at 55–85 ºC under solvent-free conditions furnished the corresponding disubstituted 1,2,3-triazoles within 30 minutes.[13]

Herein, we describe the synthesis of four 1,4,5-trisubstituted 1,2,3-triazoles (6, 7, 8 and 9 see Scheme 1) via 1,3-dipolar reaction between dimethyl acetylenedicarboxylate (DMAD) and substituted X-aryl azides 1, 2, 3 and 4.

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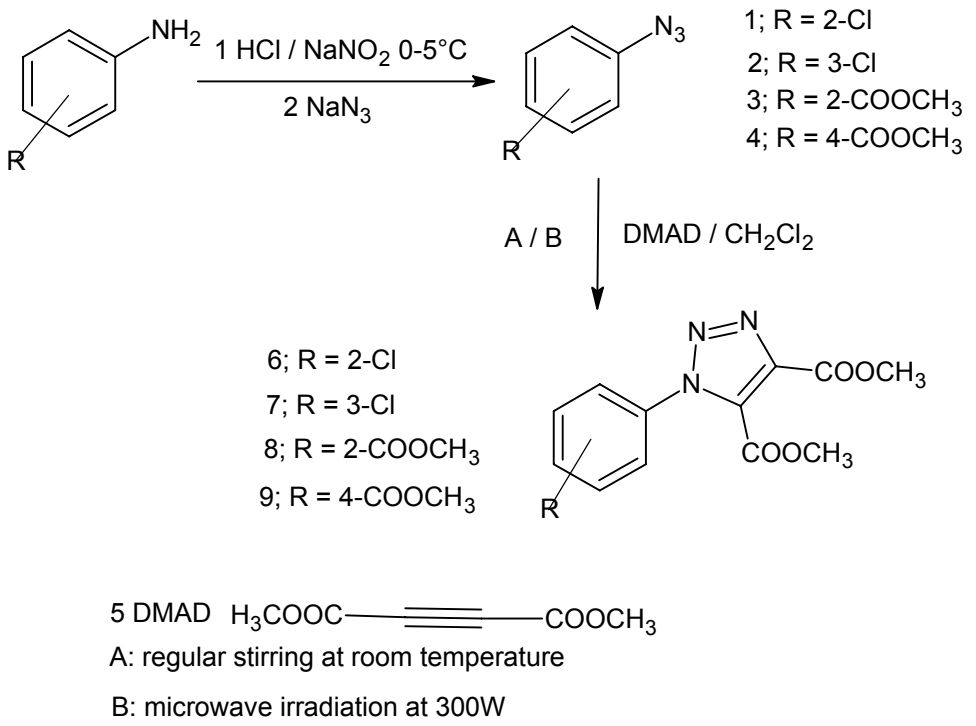


Scheme 1 – Preparation of aryl azides and 1,2,3-triazoles.

Table 1

Reaction times and yields of the 1,3-dipolar cycloaddition of substituted aryl azides with dimethyl acetylenedicarboxylate under classical conditions and under microwave (MW) irradiations

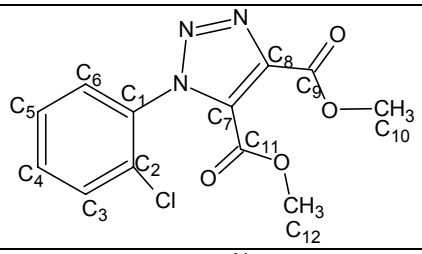
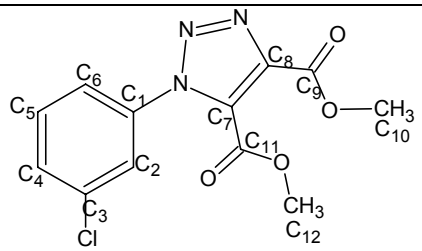
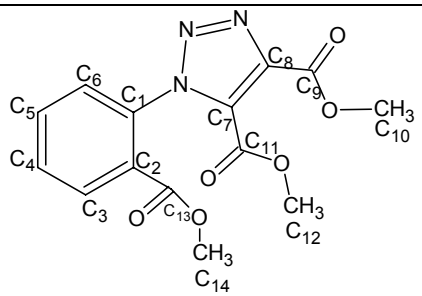
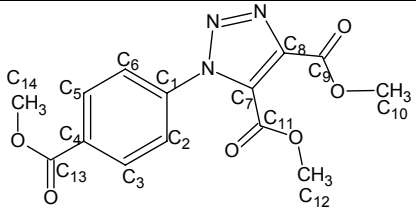
Entry	Product	Reaction time a/b	Yield (%) a/b
1		Classical; 9 days MW; 10 min	Classical; 62 MW; 80
2		Classical; 14 days MW; 11 min	Classical; 53 MW; 67
3		Classical; 7 days MW; 9 min	Classical; 87 MW; 100

Table 1 (continued)

4		Calssical; 13 days MW; 10 min	Classical; 72 MW; 85

[a] classical condition: regular stirring at room temperature.
[b] microwave irradiation at 300W.

RESULTS AND DISCUSSION

The general synthesis of the title compounds is outlined in Scheme 1. We started with the preparation of aryl azides 1-4 in the first step. The synthesis of the former products were performed in HCl (6M) at 0°C starting from the corresponding amines via their diazonium salts, according to the literature procedure.[17] The yields thus obtained are good in all cases (~85%).The azide function was confirmed by their FTIR spectra, by the presence of a strong band around 2120 cm^{-1}.

The second step consists of reacting the freshly prepared azides with dimethyl acetylenedicarboxylate (DMAD) in dichloromethan. In 1,3-dipolar cycloaddition reaction type, where the azide is the 1,3-dipole and the alkyne (DMAD) is the dipolarophile, Huisgen cycloaddition could be explained using the Frontier Molecular Orbitals (FMO) theory. The alkyne used in our work is a symmetrical dipolarophile, so the substituted aryl azide is the dipole controlling the reaction. The coefficient of (N_2) changes with respect to the substituent attached to the phenyl ring of the azide. The presence of electron-withdrawing group in *ortho*-position will increase the coefficient of (N_2) and this will decrease the energy of both HOMO and LUMO orbitals. The decrease in energy of the latters is in accord with the increase of the electronegativity of the *ortho*-substituent. As the reactions were carried out under similar conditions, the expectation of the yield and the reaction time will respect the FMO theory and accordingly the reaction time is shorter and the yield is greater, as the electron-withdrawing effect of the *ortho*-substituent increases as found practically (see Table 1).

EXPERIMENTAL

General

The chemicals were purchased from commercial supplies, and they were used without any further purification. Melting points were determined with a hot stage koffler and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer spectrometer 8000 FT-IR, as KBr pellets. ^1H and ^{13}C NMR spectra were recorded on Brüker Avance dpx 250 MHz, employing $CDCl_3$ as a solvent at room temperature. GC-MS spectra were recorded on a Shimadzu. All reactions were followed by thin layer chromatography (TLC), using (1:4 (V/V) / EtOAc–petroleum ether) as eluent, carried out on Merck silica gel 60 F254 sheets with a fluorescent indicator and were visualized under UV light (254 nm). Preparative layer chromatography (PLC) plates precoated with Kieselgel 60 F_{254} layers 0.25 mm thick. A commercial Samsung CE107B oven, 900W and 2450MHz were used for microwave experiments.

General procedure for azide synthesis

X-substituted phenyl amine (1 equivalent) in concentrated hydrochloric solution 6M (150 mL) was heated at 45°C for 30min. The mixture was cooled to (0-5°C) and then added to a solution of sodium nitrite (1,1 eq. in water (40 mL), while maintaining the temperature between (0-5°C). The resulting diazonium solution was kept cooled and added dropwise to a solution of sodium acetate (60g) and sodium azide (1,1 eq.) in water (150 mL) and the resulting mixture was stirred for 30 min. The solide was filtered off, washed with water (30 mL) then dried to give the aryl azides 1,[18] 2,[19] 3[20] and 4.[21]

General procedure for the cycoladdition reaction

Procedure for cycloaddition following the conventional stirring A

The alkyne (DMAD) (1 eq) and the aryl azide (1 eq.) were dissolved in dry CH_2Cl_2 (40 mL). This solution was stirred at room temperature, for a given time. The solvent was removed under reduced pressure and the crude product was purified by either recrystallization from an appropriate solvent compounds 6, 7 and 8 or with PLC compound 9 using 1 / 4 (v/v): EtOAC / petroleum ether system to furnish the desired 1,2,3-triazoles (6-9).

Procedure for microwave assisted heating B

The reactions were carried out in a conventional microwave oven. A mixture of aryl azides (1 eq.) and dimethyl acetylenedicarboxylate (1 eq.) were dissolved in dry dichloromethane. The resulting solution was exposed to microwave irradiation at 300W in 100 mL open flask for a few to several minutes (see Table 1). After the solvent was evaporated the crude product was treated with boiling petroleum ether to remove the unreacted azide, the resulting compounds are purified by recrystallization.

Dimethyl 1-(2-chloro phenyl)-1,2,3-tiazolo-4,5-dicarboxylate 6

Grey solid, mp = 53°C from ethanol, IR(film): υ (C-Cl) = 1068.49 cm^{-1}; υ (C=O) 1746.00 cm^{-1} ; υ (2 x C=O) 1735 cm^{-1} . ^{1}H NMR ($CDCl_3$; 250MHz): δ = 3.90 (s, 3H, CH_3); 3.98(s, 3H, CH_3); 7.44 -7.57 (m, 4H, arom). ^{13}C NMR ($CDCl_3$; 250MHz), δ =132.51 (C_1), 144.47 (C_2), 128.57 (C_3), 130.80 (C_4), 127.81(C_5), 132.16 (C_6), 143.25(C_7), 133.51 (C_8), 160.11 (C_9, C_{11}), 52.69 (C_{10}, C_{12}).GC-MS: single pic at 16.25 min, M/Z: (295, 25%), (111, 100%).

Dimethyl 1-(3-chloro phenyl)-1,2,3-tiazolo-4,5-dicarboxylate 7

Yellowish solid, mp = 120°C from ethanol, IR(film): υ (C-Cl) = 1085.85 cm^{-1}; υ (2 x C=O) 1735 cm^{-1} ; ^{1}H NMR ($CDCl_3$; 250MHz): δ = 3.90 (s, 3H, CH_3); 3.98(s, 3H, CH_3); 7.21-7.37 (m, 1H, arom); 7.38-7.50 (m, 2H, arom); 7.52-7.63 (m, 1H, arom). ^{13}C NMR($CDCl_3$; 250MHz), δ =130.68 (C_1, C_5), 122.38 (C_2), 135.25 (C_3), 124.58 (C_4, C_6), 138.83(C_7), 132.22 (C_8), 168.21 (C_9, C_{11}), 52.70 (C_{10}, C_{12}). GC-MS: single pic at 14.25 min, M/Z: (230, 100%); (77, 36%).

Dimethyl 1-[2-(methoxycarbonyl) phenyl]-1H-1,2,3-tiazole-4,5-dicarboxylate 8

Brown solid, mp = 93°C from PLC, IR(film): υ (C=O) 1720 cm^{-1} ; υ (2 x C=O) 1735 cm^{-1}.^{1}H NMR ($CDCl_3$; 250MHz): δ = 2.33 (s, 3H, CH_3); 3.75(s, 3H, CH_3); 3.98(s, 3H, CH_3); 7.32-7.46 (m, 1H, arom); 7.57-7.71 (m, 2H, arom); 7.78-7.96 (m, 1H, arom). ^{13}C NMR ($CDCl_3$; 250MHz), δ =131.24 (C_1), 133.17 (C_2), 129.84 (C_3), 128.38 (C_4), 134.84(C_5), 129.57 (C_6), 138.88(C_7), 132.84 (C_8), 160.18 (C_9, C_{11}, C_{13}), 53.38 (C_{10}, C_{12}), 52.65 (C_{14}). GC-MS: single pic at 18.50 min, M/Z: (319, 100%); (144, 80%).

Dimethyl 1-[4-(methoxycarbonyl) phenyl]-1H-1,2,3-tiazole-4,5-dicarboxylate 9

Brownish solid, mp = 84°C from PLC purification, IR(film): υ (C=O) = 1720 cm^{-1}; υ (2 x C=O) 1734 cm^{-1}; υ (C=O) 1760 cm^{-1} .^{1}H NMR ($CDCl_3$; 250MHz): δ = 3.80 (s, 3H, CH_3); 3.98(s, 3H, CH_3); δ = 2.28 (s, 3H, CH_3); δ = 7.51-7.54 (m, 2H, arom); δ = 8.10-8.15 (m, 2H, arom). ^{13}C NMR ($CDCl_3$; 250MHz), δ =132.15 (C_1, C_8), 130.86 (C_2, C_3, C_5, C_6), 131.17 (C_4), 144.50(C_7), 165.96 (C_9, C_{11}), 53.44 (C_{10}, C_{12}), 165.34 (C_{13}), 52.54 (C_{14}). GC-MS: single pic at 21 min, M/Z: (319, 35%); (260, 100%).

CONCLUSIONS

We have synthesized four 1,4,5-trisubstituted 1,2,3-triazoles via 1,3-dipolar cycloaddition reaction type. Comparison was made under two different conditions, reaction under regular stirring at room temperature versus microwave irradiation. The obtained results indicate that the microwave irradiation can significantly shorten the reaction time and can enhance the reactivity of the reactants leading to excellent yields. The presence of an electron whithdrawing effect substituent in the *ortho* position to the azide group gave the best results.

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