



SYNTHESIS OF SOME 1,4,5-TRISUBSTITUTED 1,2,3-TRIAZOLES BY 1,3-DIPOLAR CYCLOADDITION OF 2-SUBSTITUTED PHENYL AZIDES TO DIMETHYL ACETYLENE DICARBOXYLATE (DMAD), REGULAR STIRRING VERSUS MICROWAVE IRRADIATION: A COMPARATIVE STUDY

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ABSTRACT

1,4,5-trisubstituted 1,2,3-triazoles were prepared by 1,3-dipolar cycloaddition reaction of some 2-substituted phenyl azides to dimethylacetylene dicarboxylate (DMAD) under regular stirring at room temperature or under microwave irradiation. The targeted compounds were obtained in good to excellent yields. The use of microwave irradiation gives the highest yields in few minutes and proper products.

Key words: aryl azides, DMAD, 1,3-dipolar cycloaddition, microwave irradiation, 1,2,3-triazoles

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INTRODUCTION

1,2,3-triazoles are versatile compounds which are applied for strongly varying purposes, including antimicrobial¹, antibacterial², inhibitor of HIV-1 replication³ and antiallergic⁴ or potassium channel activator⁵⁻⁶, they are also used as optical brighteners, light stabilizers, fluorescent whiteners and corrosion retarding agents.⁷ The most commonly used protocol to prepare these compounds is via Huisgen's 1,3-dipolar cycloaddition of organic azides to alkynes.⁸ The drawbacks of this method are long reaction times, low yields and poor regioselectivity within unsymmetrical alkynes giving rise to a regioisomeric mixtures. Therefore alternative methods have been developed to gain in regioselectivity, time and yield by the sharpless group (the approach was termed click chemistry) and by the meldal group independently.⁹ They reported that the reaction of terminal alkynes with alkyl azides catalyzed by the Cu (I) species can be performed under mild conditions, resulting in products with high regioselectivity and quantitative yields.¹⁰ However these methods cannot be applied to Internal alkynes. It is still of interest to develop more efficient cycloaddition methods since the reactions that involves the azides or alkynes with low reactivity requires long reaction time and gives low yields.

Synthetic organic reactions performed under non-traditional conditions are gaining popularity, primarily to circumvent growing environmental concerns. Microwave-assisted synthesis is an emergent technology with a great potential for industrial applications as it dramatically reduces reaction times, improves reaction yields and uses a safe heating source¹¹. 1,3-dipolar cycloaddition was found to involve polar transition states, favorable for microwave activation¹². An example of microwave-assisted azide-alkyne cycloaddition was reported by Katrizky and Singh¹³.

In this paper we report a comparative study of the synthesis of 1,4,5,-trisubstituted 1,2,3-triazoles, using a cycloaddition reaction of 2-substituted phenyl azides to dimethyl acetylene dicarboxylate (DMAD) (scheme 1), in CH₂Cl₂ under either regular stirring or microwave heating.

EXPERIMENTAL

General

The chemicals were purchased from commercial supplies were used without any further purification. Melting points were determined with a BannedStead Elctrothermal digital melting point apparatus BI 9100, and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer onespectrometer 8000 FT-IR, as KBr pellets or in nujol mulets. ^1H and ^{13}C NMR spectra were recorded on Brüker Avance dpx 250 MHz, employing CDCl_3 as a solvent and tetramethylsilane as the internal reference at room temperature. All reactions were followed by thin layer chromatography (TLC) , 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 F₂₅₄ layers 0.25 mm thick and eluted with (1:4 (V/V) / EtOAc–petrolum ether) solvents mixture.

General procedure for azides synthesis

2-substituted phenyl azide (1equivalent) in concentrated hydrochloric solution 6M (150 ml) was heated at 45°C for 30min.the mixture was cooled to (0-5°C).To this mixture was added a solution of sodium nitrite (1,1 equivalent in (40 ml) of water while maintaining the temperature (0-5°C).The resulting diazonium solution was kept cooled and added dropwise to a solution of sodium acetate (60 g) and sodium azide (1,1 equivalent) in water (150 ml) and the resulting mixture was stirred for 30min.the solide was filtered off , washed with water (30 ml) and acidified to gives the aryl azides **1,2,3,4** and **5**.

General procedure for the cycladdition reaction

Procedure A

The alkyne (DMAD) (1 equivalent) and the aryl azides (1Equivalent) 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 PLC using 1 / 4 (v/v): EtOAC/petroleum ether system to furnish the desired 1,2,3-triazoles **2 (a-e)**.

Procedure B

The reactions were carried out in a conventional microwave oven. A mixture of aryl azides (1equivalent) and acetylene dicarboxylate (1 equivalent) were dissolved in dry dichloromethane. the resulting solution was exposed to microwave irradiation at 300W in 100ml open flask for a few to several minutes (see table 1).The crude product was treted with boiling petroleum ether to remove the unreacted azide, and purified with PLC using 1 / 4 (v/v) : EtOAC /petroleum ether system to give the title compounds as pure products.

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

White crystals, mp = 108°C from ethanol, IR(film): ν (CN) = 2235 cm^{-1} ; ν (C=O) 1735 cm^{-1} ; ^1H NMR (CDCl_3 ; 250MHz): δ = 3.80 (s, 3H, CH_3); 4.02(s, 3H, CH_3); 7.50-8.00 (m, 4H, arom). ^{13}C NMR(CDCl_3 ; 250MHz), δ =156.80, 157.40, 52.50, 54.10, 139.80, 112.00, 132.00, 129.00, 132.00, 110.00.

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

Yellow solid from ethanol, mp = 92°C. IR (film): ν (C=O) = 1755 cm^{-1} ; ν (NO_2) = 1371 cm^{-1} . ^1H NMR (CDCl_3 ; 250MHz): δ = 3.90(s, 3H, COCH_3); 4.05 (s, 3H, COCH_3); 7.75-7.90 (m, 4H, arom). ^{13}C NMR (CDCl_3 ; 250MHz), δ =159.99, 157.90, 52.99, 53.64, 129.87, 184.37, 125.83, 129.34, 134.38, 124.33

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

Pale yellow, mp = 57°C solid from ethanol. IR (film): ν (C=O) = 1742 cm^{-1} . ^1H NMR (CDCl_3 ; 250MHz): δ = 3.80(s, 3H, COCH_3); 4.05 (s, 3H, COCH_3); 7.80-8.00 (m, 4H, arom). ^{13}C NMR (CDCl_3 ; 250MHz), δ = 160.07, 157.80, 52.88, 53.34, 160.07, 157.80, 120.14, 139.14, 124.49, 127.43, 129.52, 132.94, 131.54, 127.50.

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

Yellow powder, mp = 60°C, from ethanol. IR (film): ν (C=O) = 1743 cm^{-1} . ^1H NMR (CDCl_3 ; 250MHz): δ = 3.89 (s, 3H, COCH_3); 4 (s, 3H, COCH_3); 7.25-7.70 (m, 4H, arom). ^{13}C NMR (CDCl_3 ; 250MHz): δ =208.00, 52.82, 53.53, 139.19, 160.04, 158.22, 118.00, 132.50, 127.5; 128.

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

Transparent crystals, mp = 49°C, from ethanol. IR (film): ν (C=O) = 1471 cm⁻¹. ¹H NMR (CDCl₃; 250MHz): δ =2.05(s, 1H); 3.80(s, 3H); 4(s,3H); 7.20-7.55(m, 4H). ¹³C NMR (CDCl₃; 250MHz): δ =160.21; 158.58; 52.14; 53.95; 133.06; 17.18; 134.48; 138.41; 135.21; 131.23; 131.09; 126.73.

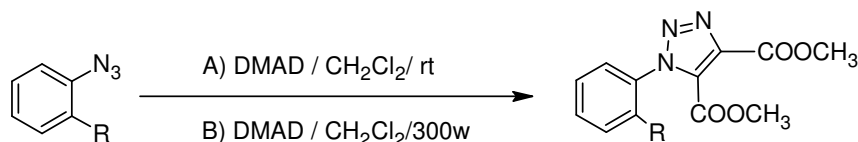
RESULTS AND DISCUSSION

We are interested in extending the 1,3-dipolar cycloaddition reaction of *O*-nitro phenyl azide with dimethyl acetylene dicarboxylate (DMAD) [14] to other -substituted aryl azides and improving the yields and decreasing the reactions times.

Azides were prepared using the well known protocol of Noelting [15], from the corresponding amines via their diazonium salts. The freshly prepared aryl azides were reacted with DMAD at room temperature for a definite time to yield the expected triazoles adducts 2 (a-e) in varying yields, (see table 1).

As can be seen from table 1, cycloaddition at room temperature was monitored by TLC, and the reaction was very slow.

On the other hand, carrying out the above mentioned reaction in a traditional microwave oven yields the same products but in much better yields and in very short reactions times as shown in table 1.



R = NO₂, CN, CF₃, F, CH₃

a: R = CN

b: R = NO₂

c: R = CF₃

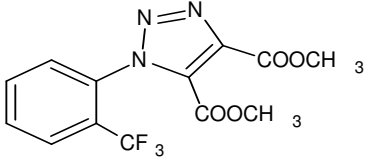
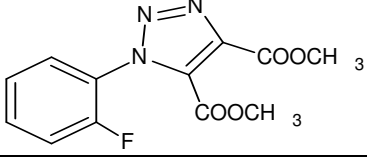
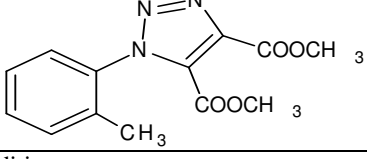
d: R = F

e: R = CH₃

Scheme 1: synthesis of 1,4,5-disubstituted 1,2,3-triazoles via 1,2,3-dipolar cycloaddition of ortho aryl azide and dimethyl acetylene dicarboxylate

Table-1: reaction times and yields of the 1,3-dipolar cycloaddition of 2-phenyl azide with DMAD

Entry	Product	Reaction time(days /min) ^{a/b}	Yield (%) ^{a/b}
1		4,3 / 14	75 / 90
2		15 / 29	57 / 86

3		11 / 8	68 / 88
4		1 / 8	89 / 98
5		9 / 8	10 / 78

^a regular stirring conditions

^b microwave conditions

CONCLUSION

The cycloaddition reaction of various 2-substituted phenyl azides to DMAD was studied. Comparison was made of two different conditions, reaction under regular stirring at room temperature versus microwave irradiation. We have found that performing the cycloaddition under the former condition is a very convenient route to synthesize 1,4,5-trisubstituted 1,2,3-triazoles, because it increases significantly the reaction yield in comparison to regular stirring, and reduces the reaction time from several days to few minutes.

Studies to determine the effect of the substituent position on the reaction times and yields are currently underway in our lab.

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