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CHEMOSELECTIVE REACTION OF ARYL AZIDES WITH ETHYL 3-OXO-4-(TRIPHENYLPHOSPHOR-ANYLIDENE)BUTANOATE

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The reaction of aryl azides with ethyl 3-oxo-4-(triphenylphosphoranylidene)butanoate has been studied under different conditions and it was found that the reaction occurs chemoselectively to form one of two possible isomers. Novel (1H-1,2,3-triazol-5-yl)acetic acids have been synthesized.

Keywords: azides, 1H-1,2,3-triazole, heterocyclizations, chemoselectivity.

Following the recent discovery of biological activity and other practically useful properties amongst many 1,2,3-triazole derivatives the amount of work relating to these compounds and to satisfactory synthetic methods has grown (as seen in reviews discussing these topics [1-5]).

One basic method for constructing a 1,2,3-triazole ring is the reaction of azides with acetylenes or activated methylene compounds [1-5]. The cycloaddition of azides to acetylenes is generally used in the synthesis of triazole fragments with identical substituents in positions 4 and 5 since the use of unsymmetrical alkynes potentially leads to formation of two regioisomers. The reaction of azides with activated methylene compound anions (generally containing a CO or CN group near the carbanion center) or phosphorus ylides with a keto group in the α-position shows higher regioselectivity as a result of a closely controlled distribution of charges [3]. However, in such reactions secondary processes are possible, e.g. a diazo exchange with reduction of the azide group to an amino group [3]. It should be noted that reactions of azides with compounds having several potential carbanion centers have not been reported in the literature.

In this publication we report the results of a study of the reaction of aryl azides with ethyl 3-oxo-4-(triphenylphosphoranylidene)butanoate (**1**). Through a marked polarization of the C=P bond in such ylides the negative charge is localized on an oxygen atom and a 1,3-dipolar cycloaddition of azide to the enol form of ylide **1b** occurs with a subsequent loss of triphenylphosphine oxide [6]. It should be noted that a non-synchronous anion mechanism involving addition in the first stage of the terminal nitrogen atom of the azide group to ylide **1a** and subsequent attack at the carbonyl group gives a similar result. It should also be noted that an alternative reaction route *via* attack of the ylide fragment by the azide group is possible. In a series of examples phosphazines and diazo compounds are generated as a result of a 1,3-dipolar addition of azide to the strongly polarized C=P bond rather than the C=C bond [6].

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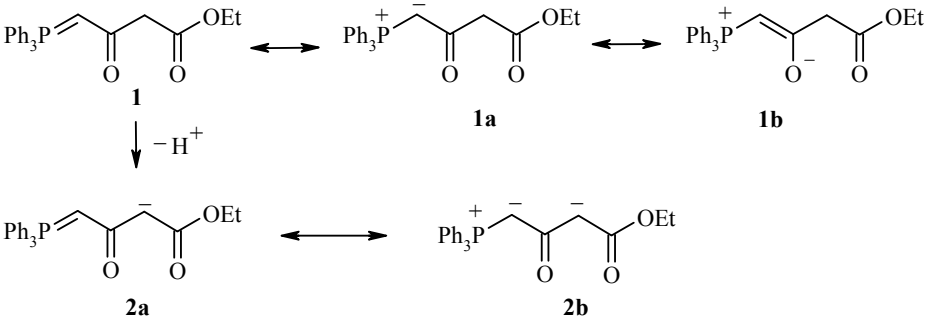
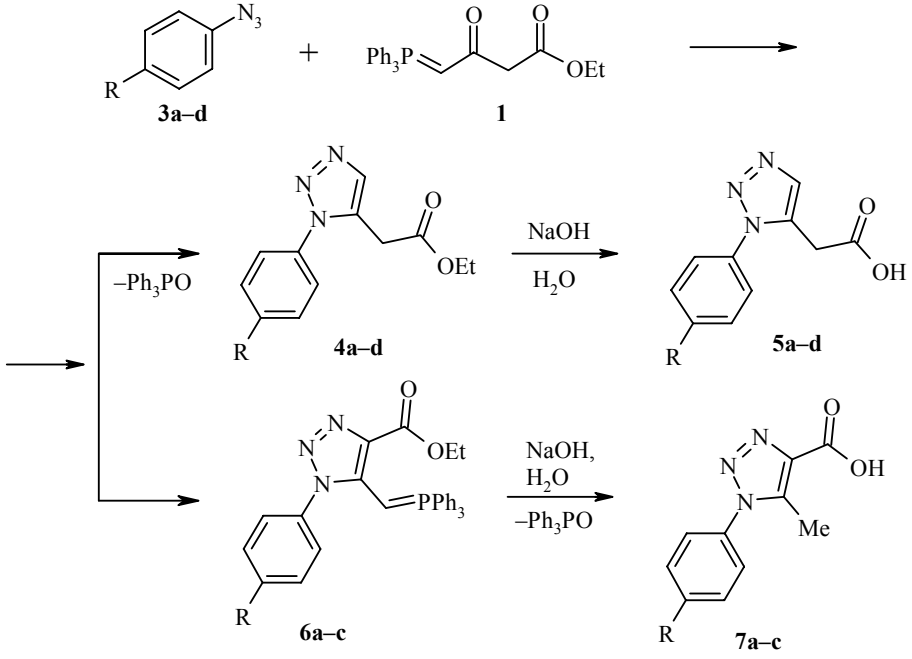
The structure of the deprotonated compound **1** can be represented by the resonance structures **2a,b** [7] implying a possible electrophilic attack at both reaction centers (positions 2 and 4).



Hence in treating ylide **1** with the aryl azides **3** attack of the azide group can occur at position 2 or 4. The study [8] reports the reaction of compound **1** with C-electrophiles at position 2. In our case the electrophilic center is the terminal nitrogen atom of the azide group.

We have studied the reaction of azides **3** with ylide **1** in various solvents and bases including benzene, Et_3N in benzene, NaH in benzene, NaOMe in methanol, and KOH in DMSO. It was found that carrying out the reaction in benzene gave the triazolylacetates **4a-d** which underwent hydrolysis to acids **5a-d** without their separation.



3–7 a R = H, **b** R = Me, **c** R = Cl, **d** R = NO_2

The reaction occurred by the same route if base (Et_3N or NaH) was added to the reaction mixture. However, in the case of NaH the yields of compound **5** were somewhat decreased and, by contrast, use of triethylamine increased the reaction rate and the yields (Table 1). In all cases the reactions were carried out at room temperature with some exothermic effect. A decrease in the yield of triazole **5d** in the presence of base is related to concurrent reduction reactions of the starting 4-nitrophenyl azide **3d** as has been noted in the literature [9].

TABLE 1. Yields of Compounds **5a-d** under Different Reaction Conditions*

Compound	Yield, %				
	benzene	Et_3N in benzene	NaH in benzene	NaOMe in methanol	KOH in DMSO
5a	56	74	49	7*[2]	—
5b	57	77	54	8*[2]	—
5c	64	80	58	13*[3]	—
5d	71	65	36	—	—

* Reaction carried out at 75-80ºC in methanol at reflux temperature.
*[2] Acids **7a,b** were obtained in trace amounts.
*[4] Compound **7c** (6%) also observed.

Attempts to change the reaction route and to prepare compounds **6** were unsuccessful. The influence of concurrent reactions became more marked with increase in the basicity of the medium. The use of strongly basic media (NaOMe in methanol or KOH in DMSO) led to tarring of the reaction mixture. Only in the single example of the use of the 4-chlorophenyl azide **3c** and with the reaction carried out in methanol in the presence of MeONa was a low yield of the ester **6c** obtained and this was identified as the acid **7c** [10] formed as a result of hydrolysis of the $Ph_3P{=}CH$ group. Use of ^{1}H NMR spectroscopy also showed trace amounts of the acids **7a,b**.

In all the experiments the reaction products were analyzed by chromato-mass spectrometry. Aromatic amines were identified as secondary products.

A specific drawback of the synthetic methods using phosphorus ylides is that the reaction product has to be separated from triphenylphosphine oxide which is formed during the reactions. Hence the method discussed here can conveniently be used in the synthesis of triazolyl-containing acids and amines which can be readily separated *via* a water soluble salt.

It should be noted that the triazolylacetic acids **5a-d** are quite stable and survive heating in solution to 80ºC without decarboxylation (which is noted for similarly structured acids [11]).

Thus it was shown that cyclization of acyl azides with ethyl 3-oxo-4-(triphenylphosphoranylidene)-butanoate occurs chemoselectively. The novel (1H-1,2,3-triazol-5-yl)acetic acids obtained are promising reagents for organic synthesis.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Unity Plus400 (400 MHz) instrument using DMSO-d_6 and with TMS as internal standard. Mass spectra were taken on an Agilent 1100 LC/MSD chromato-mass spectrometer using chemical ionization.

The starting ylide **1** was synthesized by reaction of 4-chloroacetoacetic ester with triphenylphosphine and subsequent treatment with base [12]. Azides **3a-d** were prepared by method [13].

Synthesis of (1-Aryl-1H-1,2,3-triazol-5-yl)acetic Acids 5a-d (General Method). Aryl azide **2** (0.1 mol) and triethylamine (14 ml) were added with stirring to a solution of ylide **1** (3.9 g, 0.1 mol) in benzene (50 ml). The reaction mixture was heated for 2 h, a solution of NaOH (14%, 50 ml) was added, and the product was heated for a further 2 h. The separated aqueous layer was washed with a small amount of benzene and acidified. The precipitated acid **5** formed was filtered off and recrystallized from ethanol.

The remaining experiments (see Table 1) were carried out similarly using equimolar amounts of reagents and base in the corresponding solvent (50 ml).

(1-Phenyl-1H-1,2,3-triazol-5-yl)acetic Acid (5a). Yield 74%; mp 128-129ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.77 (2H, s, CH_2); 7.48-7.64 (5H, m, H Ph); 7.73 (1H s, H Tr); 12.50 (1H, br. s, COOH). Mass spectrum, *m/z* (I_{rel}, %): 204 $[M+H]^+$. Found, %: C 58.88; H 4.51; N 20.57. $C_{10}H_9N_3O_2$. Calculated, %: C 59.11; H 4.46; N 20.68.

[**1-(4-Methylphenyl)-1H-1,2,3-triazol-5-yl]acetic Acid (5b)**. Yield 77%; mp 149-150ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 (3H, s, CH_3); 3.72 (2H, s, CH_2); 7.37 (4H, m, H Ar); 7.70 (1H, s, H Tr); 12.67 (1H, br. s, COOH). Mass spectrum, *m/z* (I_{rel}, %): 218 $[M+H]^+$. Found %: C 60.76; H 5.23; N 19.22. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.82; H 5.10; N 19.34.

[1-(4-Chlorophenyl)-1H-1,2,3-triazol-5-yl]acetic Acid (5c). Yield 80%; mp 185-186ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.80 (2H, s, CH_2); 7.57 (2H, d, *J* = 8.8, H-3,5 Ar); 7.61 (2H, d, *J* = 8.8, H-2,6 Ar); 7.73 (1H, s, H Tr); 12.68 (1H, br. s, COOH). Mass spectrum, *m/z* (I_{rel}, %): 238 $[M+H]^+$. Found, %: C 50.30; H 3.27; N 17.75. $C_{10}H_8ClN_3O_2$. Calculated, %: C 50.54; H 3.39; N 17.68.

[1-(4-Nitrophenyl)-1H-1,2,3-triazol-5-yl]acetic Acid (5d). Yield 65%; mp 219-220ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.80 (2H, s, CH_2); 7.73 (1H, s, H Tr); 8.03 (2H, d, *J* = 8.8, H-3,5 Ar); 8.46 (2H, d, *J* = 8.8, H-2,6 Ar); 12.68 (1H, br. s, COOH). Mass spectrum, *m/z* (I_{rel}, %): 249 $[M+H]^+$. Found, %; C 48.31; H 3.02; N 22.39. $C_{10}H_8N_4O_4$. Calculated, %: C 48.39; H 3.25; N 22.57.

5-Methyl-1-phenyl-1H-1,2,3-triazole-4-carboxylic acid (7a). Yield 2%; mp 147-148ºC [14-16].

5-Methyl-1-(4-methylphenyl)-1H-1,2,3-triazole-4-carboxylic acid (7b). Yield 2%; mp 183-184ºC [16].

1-(4-Chlorophenyl)-5-methyl-1,2,3-triazole-4-carboxylic acid (7c). Yield 6%; mp 213-214ºC [15, 16].

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