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REACTIONS OF ARYL AZIDES WITH α-KETO PHOSPHORUS YLIDES[1]

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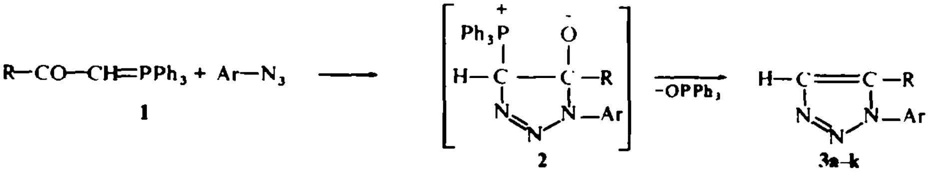
Abstract—Acylmethylenetriphenylphosphoranes react with aryl azides in refluxing benzene to give 1-aryl-5-substituted-1,2,3-triazoles exclusively. The regiochemistry of the reaction was resolved by comparison of the triazoles with authentic samples, prepared by the Dimroth method. From the kinetic point of view, the reaction is accelerated by electron-withdrawing substituents on the azide and electron-releasing substituents on the ylide. The polarity of the solvent has only a small effect on the reaction rate. Finally, the low entropies of activation support a concerted cycloaddition in the first step of the reaction.

The addition of aryl azides to C—C triple bonds,[2] and the condensation of aryl azides with active methylene compounds in the presence of a base[3] are two general methods for the synthesis of 1-aryl-1,2,3-triazoles. As an extension of our work in the ylide field,[4, *] we have developed a third general synthetic route to 1-aryl-1,2,3-triazoles by reacting α-keto phosphorus ylides with aryl azides, according to the following scheme:



This reaction scheme has already been found to be of general value for the preparation of triazoles having an electron-withdrawing group (sulfonyl) in the 1-position.[5] Aryl azides although less reactive than sulfonyl azides, readily combine with **1** in refluxing benzene solution to give **3** in good yields (Table 1).

The triazoles **3a–k** exhibit several IR absorptions in the region 950–1120 cm^{-1} which have been tentatively assigned by several authors[6] to vibrations of the triazole nucleus. Much more typical for characterizing our products, however, is the triazole =C—H stretching vibration at 3100–3140 cm^{-1}. Also typical are the triazole ring proton signals in the NMR spectra at about δ 7·5–8·1.

Structural proof for **3** was obtained through an independent synthesis by reacting the β-keto esters **4** with aryl azides in the presence of sodium ethoxide, followed by decarboxylation of **5** (see experimental section). This reaction, referred to as the

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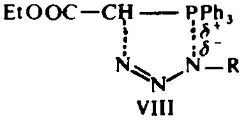
[*] The structures indicated for the transition states VIII and IX in the Tetrahedron publication have been incorrectly printed and should read:



VIII

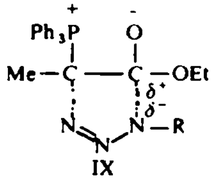


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TABLE 1. MONO- AND BIS-1-ARYL-5-SUBSTITUTED-1,2,3-TRIAZOLES

	Triazole 3†		Reaction conditions	Yield	Recrystn solvent	m.p.
	R	Ar		%		°C
a	CH_3-	$p\text{-}NO_2-C_6H_4-$	1/2 hr, 80°	73	methanol	139–140·5
b		$p\text{-}Br-C_6H_4-$	3 months, 20°	66	aq. methanol	98·5–99·5
c		$p\text{-}CH_3O-C_6H_4-$	1 day, 80°	54	n-hexane	43·5–45
d	C_6H_5-	$p\text{-}NO_2-C_6H_4-$	1 hr, 80°	77	methanol	162·5–164
e		$p\text{-}Br\text{-}C_6H_4$	4 hr, 80°	90	aq. methanol	90–91·5 and 104·5–106*
f		C_6H_5-	2 days, 80°	80	methanol	116–117
g		$p\text{-}CH_3O-C_6H_4-$	3 days, 80°	54	ether	84–85
h	$p\text{-}NO_2-C_6H_4-$	$p\text{-}NO_2-C_6H_4-$	2 days, 80°	98	methanol	200·5–202
i		$p\text{-}Br-C_6H_4-$	2 days, 80°	85	chloroform-n-hexane	173–174
j		C_6H_5-	6 days, 80°	67	aq. methanol	150–151
k		$p\text{-}CH_3O-C_6H_4-$	10 days, 80°	70	methanol	145·5–146·5
l	CH_3-		5 hr, 80°	83	methanol	235·5–236
m	C_6H_5		2 days, 80°	91	benzene	229·5–230

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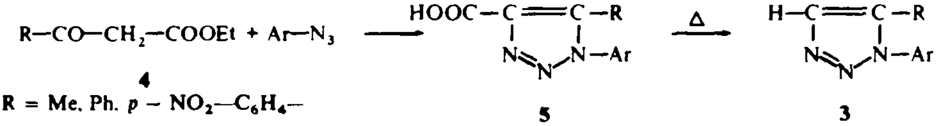
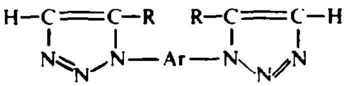
* This triazole seems to exist in two different crystalline forms with different m.p. and slightly different IR (KBr) spectra. The NMR spectra in $CDCl_3$ solution are the same.

† C, H, and N analyses of the unknown triazoles were within 0·2–0·4%.



Dimroth reaction,[3] is known to afford a triazole with the R substituent in the 5-position. The identity of the triazoles from **1** with those from **4** adequately demonstrates the regiochemistry[7] of the reaction, that is, the exclusive formation of 1,5- instead of 1,4-disubstituted triazoles.

Since the additions occur only in one direction, the reactions of bis-azides with **1** provide a simple and efficient route to symmetrical bis-1,2,3-triazoles (eg **3l, m**). The results obtained with 1,4-diazidobenzene are given in Table 1.



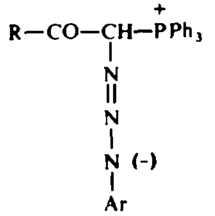
3l m

The reaction conditions listed in Table 1 indicate that triazole formation is accelerated either by introducing electron-withdrawing substituents in phenylazide or by using an ylide of stronger nucleophilicity. The data are consistent with the following two reactivity sequencies:

$$\text{azide Ar}: p\text{-NO}_2\text{—C}_6\text{H}_4\text{—} > p\text{-Br—C}_6\text{H}_4\text{—} > \text{C}_6\text{H}_5\text{—} > p\text{-CH}_3\text{O—C}_6\text{H}_4\text{—}$$

$$\text{ylide}: \text{R}: \text{CH}_3\text{—} > \text{C}_6\text{H}_5\text{—} > p\text{-NO}_2\text{—C}_6\text{H}_4\text{—}$$

These findings, however, do not elucidate the mechanism of the formation of **2**, since either a two step addition, via intermediate **6**, or a concerted cycloaddition, via transition state **7**, is consistent with the observed acceleration effects. In order to differentiate between both mechanisms, we focussed on the kinetics of the reaction of phenyl azide with benzoylmethylenetriphenylphosphorane (**1**, R = Ph) in three different solvents. The second order rate constants and the activation parameters are recorded in Table 2. It is interesting to note that the reaction rate is only slightly enhanced in a more polar solvent. This is logical if one considers the ylide as existing essentially in its enolate structure, a conclusion supported by the large displacement of the C═O absorption in the IR spectrum (at 1520 cm^{-1}). In this respect, the conversion of **1** into **2** is associated with only a very small increase in charge, so that



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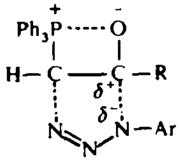

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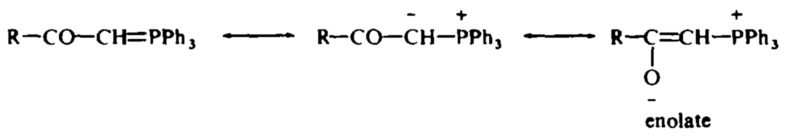

Table 2. Rate constants and activation parameters for the reaction of **1**, R = Ph with Ph-N$_3$ in different solvents*

Solvent (dielectric constant)	T °C	$10^3 k_2$ sec^{-1} l mol^{-1}	ΔE kcal mol^{-1}	$\Delta S^{\ddagger}$ (at 80°) e.u.
Toluene	70·0	0·46	15·0 ± 0·1	− 33 ± 0·3
(2·38)	80·0	0·89		
	90·0	1·68		
	100·0	2·73 (2·70)		
DMF	70·0	0·625	17·0 ± 0·1	− 26 ± 0·3
(36·7)	80·0	1·18 (1·21)		
	90·0	2·27		
	100·0	4·56		
	110·0	8·16		
DMSO	80·0	1·65 (1·69)		
(48·9)				

* 1,5-Diphenyltriazole was isolated in 75 and 67% yield from the reaction in DMF and DMSO respectively.

solvation changes during the rate determining step are practically negligible. It is therefore not surprising that almost the same entropies of activation are obtained in two solvents of quite different polarity: toluene and DMF. To account for the low entropy values, we regard the reaction as a concerted cycloaddition of the azide onto the C—C double bond of the ylide, proceeding via transition state **7**. The parallelism between α-ester phosphorus ylides and the classic dipolarophiles in their behaviour towards azides has recently been described.[4]

EXPERIMENTAL

All mg ps were obtained on a Leitz apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 521 spectrometer. NMR spectra were recorded with a Varian A-60 spectrometer using TMS as an internal reference.

Phosphorus ylides. The ylides **1** were prepared by treating the respective phosphonium salts with an aqueous solution of Na_2CO_3 or NaOH (salt method). They were carefully recrystallized from the appropriate solvent and gave the following m.p. and IR (KBr) C=O absorptions:

1, R = Me: 206–209° (from MeOH, lit.[8] 205–206°), 1540 cm^{-1}

1, R = Ph: 189·5–190° (from benzene, lit.[8] 178–180°), 1520 cm^{-1}

1, R = p-NO_2—C_6H_4—: 163–164° (from EtOAc, lit.[9] 156–157°), 1520 cm^{-1}.

General procedure for the synthesis of 1*-aryl-*1,2,3*-triazoles* **3**. The ylide **1** (0·02 mole) was allowed to react with 0·02 mole of the mono-azide or 0·01 mole of the bis-azide in 100 ml of refluxing benzene. After complete reaction (checked by IR) the solvent was removed with a rotary evaporator and the residue crystallized from MeOH or aqueous MeOH (except for **3g** which was fractionally crystallized from ether, and **3c** which was distilled off (195–200°/4 mm) after removing the triphenylphosphine oxide by precipitation in ether). The bis-triazoles **3l,m** partially precipitated from the cold reaction mixture.

Synthesis of triazoles 3 by the Dimroth method. Four of our triazoles were reported in the literature: **3a**[10] (m.p. 138–139°), **3b**[11] (m.p. 97°, the 1,4-isomer has m.p. 164°), **3d**[10] (m.p. 162–163°) and **3f**[12] (m.p. 112° the 1,4-isomer has m.p. 184–185°). The other, unknown triazoles were prepared as follows. Equimolecular amounts (0·04 mole) of aryl azide, β-keto ester **4** and NaOEt were refluxed in 75 ml EtOH for 2 hr, then heated for another hr with 75 ml of added water. The reaction mixture was poured into cold water, acidified with HCl, and the ppt was filtered off, recrystallized from water and dried.

For the condensation reactions with *p*-methoxyphenyl azide, a slightly modified procedure was used. A soln of 0·04 mole of the azide in 50 ml of dry ether was added to an equimolecular mixture of **4** and NaOEt in 75 ml EtOH and the reaction temp was maintained at about 50° till sufficient ppt was formed. The reaction was then worked up in the same way as described above. For the condensation of *p*-methoxyphenyl azide with *p*-nitrobenzoylacetate a 24 hr heating time at 75° was necessary. The following yields and m.p. for the 1-aryl-5-substituted-1,2,3-triazole-4-carboxylic acids **5** were obtained:

5c: 62%, 169–170°; **5e**: 60%, 162–164° (dec.); **5g**: 52%, 174–175° (dec.); **5h**, 100%, 169–170°; **5i**, 93%, 171–172°; **5j**: 76%, 161–163° (dec); **5k**: 62%, 112–113·5° (21% of starting acid was recovered).

The triazole-4-carboxylic acids **5** were converted quantitatively into **3**, when heated above their m.p. until gas evolution ceases.

Kinetic measurements, using IR techniques. Equimolecular mixtures of **1** (R = Ph) and phenyl azide were dissolved in the appropriate solvents. The two solns were allowed to come separately to thermal equilibrium in the thermostat and then mixed. The reaction was followed by recording the disappearance of the azide absorption (at *ca* 2130 cm^{-1}) in the IR spectrum. Azide concentrations were determined from the observed absorption using a calibration curve. By plotting 1/(azide) *vs* time, linear plots up to 80% conversion were obtained. The second order rate constants were determined from the slopes of the linear plots. Measurements in toluene and DMF were made at several temps and the energies of activation were determined graphically from log k_2 versus 1/T. The entropies of activation were calculated from the rate constants at 80·0° using the following equation:

$$\Delta S^{\ddagger} = 4{\cdot}576 \log k_2\,(\text{sec}^{-1}\,\text{l mole}^{-1}) - 49{\cdot}14 - 4{\cdot}576 \log T + \Delta E/T$$

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REFERENCES

[1] Presented in part at the *2nd International Symposium on Heterocyclic Chemistry*. Montpellier, France, July (1969)

[2] G. L'abbé, *Chem. Rev.* **69**, 345 (1969)

[3] O. Dimroth, *Chem. Ber.* **35**, 1029 (1902); *Ibid.* **35**, 4041 (1902); For a review on the Dimroth reaction, see G. L'abbé, *Ind. Chim. Belge* in press

[4] G. L'abbé and H. J. Bestmann, *Tetrahedron Letters*, 63 (1969); G. L'abbé, P. Ykman and G. Smets, *Bull. Soc. Chim. Belges* **78**, 147 (1969); *Tetrahedron* **25**, 5421 (1969)

[5] G. R. Harvey, *J. Org. Chem.* **31**, 1587 (1966)

[6] L. W. Hartzel and F. R. Benson, *J. Am. Chem. Soc.* **76**, 667 (1954); E. Lieber, C. N. R. Rao, T. S. Chao and H. Rubinstein, *Canad. J. Chem.* **36**, 1441 (1958)

[7] For a definition of this term, see A. Hassner, *J. Org. Chem.* **33**, 2684 (1968)

[8] F. Ramirez and S. Dershowitz, *Ibid.*, **22**, 41 (1957)

[9] S. Fliszar, R. F. Hudson and G. Salvadori, *Helv. Chim. Acta* **46**, 1580 (1963)

[10] R. Huisgen, L. Möbius and G. Szeimies, *Chem. Ber.* **98**, 1138 (1965)

[11] H. El. Khadem, H. A. R. Mansour and M. H. Meshreki, *J. Chem. Soc.* C, 1329 (1968)

[12] W. Kirmse and L. Horner, *Liebigs Ann.* **614**, 1 (1958)