Tetrahedron. Vol. 27, pp. 5623 to 5629. Pergamon Press 1971. Printed in Great Britain

REACTIONS OF CARBONYL AZIDES WITH α-KETO PHOSPHORUS YLIDES

SYNTHESIS OF N-2 ACYL AND N-2 CARBETHOXY-1,2,3-TRIAZOLES

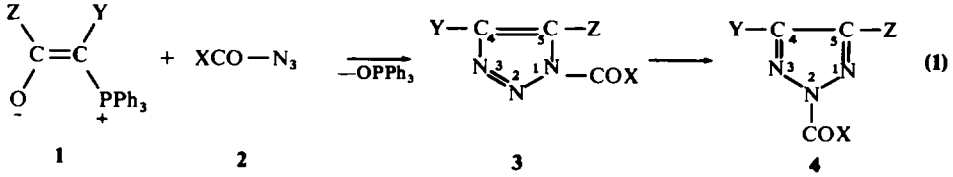
P. YKMAN, G. L'ABBÉ* and G. SMETS

Department of Chemistry, Laboratory of Macromolecular Chemistry,
University of Louvain, Celestijnenlaan 200-F, B-3030 Heverlee, Belgium

(Received in the UK 16 *June* 1971; *Accepted for publication* 18 *July* 1971*)*

Abstract—A general method for the synthesis of N-2 acyl and N-2 carbethoxy-1,2,3-triazoles is provided by the title reaction. The corresponding N-1 triazoles were shown to be the precursors of the N-2 triazoles and their respective regiostructures were elucidated by NMR. New kinetic data are presented which fully support a concerted mechanism for the cycloaddition step.

KETO-STABILIZED phosphorus ylides, which have been demonstrated recently[1] to exist essentially or exclusively in the *cis*-enolate configuration (**1**). are suitable starting materials for the synthesis of *vic*-triazoles. Sulfonyl azides produced 1-sulfonyl-triazoles.[2] and aryl azides furnished the same 1-aryltriazoles[3] as obtained by an independent route of known regiochemistry.[4] In a preliminary communication[5] we have reported that acyl azides and ethyl azidoformate also react with α-ketophosphoranes (**1**) to give first 1-acyl and 1-carbethoxytriazoles (**3**). but that the latter isomerize to the N-2 derivatives (**4**) under the basic reaction conditions (eq. 1). We have shown that path **3** → **4** is an intermolecular process and occurs under the influence of the ylide as base. In this paper we emphasize the synthetic consequences of our findings and report the results of our kinetic study.

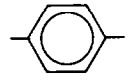
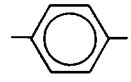
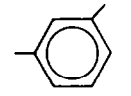


1 **2** **3** **4** (1)

Synthesis. regiochemistry and hydrolysis

When equimolar amounts of **1** and **2** were allowed to react in CH_2Cl_2 or C_6H_6 solution at room temp to completion. and the reactions then worked up in the usual way by crystallization. the isolated triazoles were all found to have structure **4**. Table 1 gives a summary of the results. Several N-1 substituted triazoles (**3**) were observed in the NMR spectrum during the course of the reaction, or even isolated (see examples **3n** and **3t** in the exp. section) when the reaction was worked up prior to completion. These helped to elucidate the regiochemistry of the triazoles. a point

TABLE 1. N-2 ACYL AND N-2 CARBETHOXY-1,2,3-TRIAZOLES

	X	Triazole 4 Y	Z	Reaction time at room temp	Yield %	Recrystn solvent	m.p.
a	*m*-$NO_2C_6H_4$	Me	Me	2 hr	79	$CHCl_3$-n-hexane	140·5–142
b	Ph	H	Me	2 days	50	ether	66·5– 68
c	*p*-$NO_2C_6H_4$	H	Me	1 day	65	$CHCl_3$-n-hexane	147–148
d	*m*-$NO_2C_6H_4$	H	Me	1 day	60	CH_2Cl_2-n-hexane	110·5–113
e	*p*-ClC_6H_4	H	Me	2 days	79	CH_2Cl_2-n-pentane	110·5–112
f	*m.p*-$Cl_2C_6H_3$	H	Me	1 day	64	CH_2Cl_2-n-pentane	109–110
g	*p*-$CH_3OC_6H_4$	H	Me	7 days	24	ether	51·5–53
h†		H	Me	1 day	60	C_6H_6	191–193·5
i	Ph	H	Ph	10 days	49	CH_2Cl_2-n-hexane	89–90
j	*p*-$NO_2C_6H_4$	H	Ph	1 day	68	C_6H_6	154–155
k	*m*-$NO_2C_6H_4$	H	Ph	1 day	77	C_6H_6	150–152
l	*p*-ClC_6H_4	H	Ph	5 days	56	CH_2Cl_2-n-pentane	118·5–119·5
m	*m.p*-$Cl_2C_6H_3$	H	Ph	1 day	80	$CHCl_3$-n-pentane	136–137
n	*p*-$CH_3OC_6H_4$	H	Ph	2 weeks	75	ether	103–104
o†		H	Ph	10 days	76	C_6H_6	221·5–222
p†		H	Ph	10 days	62	C_6H_6	156·5–158
q	OEt	H	Ph	2 days	46	MeOH	59·0– 59·5
r	*m*-$NO_2C_6H_4$	H	*p*-$NO_2C_6H_4$	20 days	43	CH_2Cl_2	190–192
s	*p*-ClC_6H_4	H	*p*-$NO_2C_6H_4$	1 month	29	CH_2Cl_2-n-hexane	166·5–168
t	OEt	H	*p*-$NO_2C_6H_4$	2 weeks	76	C_6H_6	149–150

† The examples **4h, o, p** are bistriazoles derived from bisazides of type $N_3CO—X—CON_3$

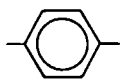
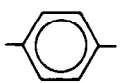
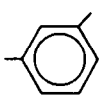
of particular importance. The characteristic NMR data in Table 2 are used in the following arguments to distinguish structures **4** from **3**:

(1) Triazole **4a** shows a singlet absorption at τ7·60 which integrates to 6 hydrogens (two Me groups), thereby demonstrating the symmetrical constitution of the molecule.

(2) The examples **4b–h** are identified by the following two criteria:[6, 7]—they exhibit singlet absorptions for the H and Me substituents, whereas splitting (J_{HMe} of about 1 Hz) occurs for the corresponding isomers of structure **3**—the Me absorptions near τ7·55 are shielded by about 0·2 ppm with respect to those in **3** (the latter are deshielded by the anisotropic C=O function in the 1-position).

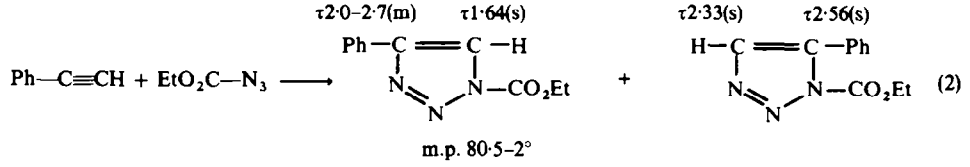
(3) The compounds **4i–q** have a phenyl substituent in the 5-position which interacts by resonance with the triazole nucleus and therefore gives rise to a splitting of the *ortho* as opposed to the *meta–para* protons. When located in the sterically hindered 5-position of **3**, the phenyl group is twisted out of the heterocyclic plane and, hence, is known[8] to resonate as a more or less sharp singlet. The nonidentity of triazole **4q**

TABLE 2. NMR DATA OF THE TRIAZOLES†

	X	Y	Z	Solvent	Triazole 3 Y	Triazole 3 Z	Triazole 4 Y	Triazole 4 Z
a	*m*-$NO_2C_6H_4$	Me	Me	$CDCl_3$	7·64(s)	7·40(s)	7·60(s)	7·60(s)
b	Ph	H	Me	$CDCl_3$			2·25(s)	7·57(s)
c	*p*-$NO_2C_6H_4$	H	Me	$CDCl_3$		7·33(d. 1 Hz)	2·15(s)	7·50(s)
d	*m*-$NO_2C_6H_4$	H	Me	$CDCl_3$			2·15(s)	7·50(s)
e	*p*-ClC_6H_4	H	Me	$CDCl_3$		7·36(d. 1 Hz)	2·23(s)	7·54(s)
f	*m.p*-$Cl_2C_6H_4$	H	Me	$CDCl_3$			2·23(s)	7·53(s)
g	*p*-$CH_3OC_6H_4$	H	Me	$CDCl_3$	2·45(q. 1 Hz)	7·39(d. 1 Hz)	2·30(s)	7·55(s)
h		H	Me	$CDCl_3$			2·15(s)	7·50(s)
i	Ph	H	Ph	$CDCl_3$			1·77(s)	2·0–2·75(m)
j	*p*-$NO_2C_6H_4$	H	Ph	$CDCl_3$			1·70(s)	1·95–2·6(m)
k	*m*-$NO_2C_6H_4$	H	Ph	$CDCl_3$			1·64(s)	1·90–2·60(m)
l	*p*-ClC_6H_4	H	Ph	$CDCl_3$			1·82(s)	2·0–2·7(m)
m	*m.p*-$Cl_2C_6H_3$	H	Ph	$CDCl_3$		2·57(s)	1·75(s)	2·0–2·6(m)
n	*p*-$CH_3OC_6H_4$	H	Ph	$CDCl_3$	2·19(s)	2·59(s)	1·77(s)	1·9–2·6(m)
o		H	Ph	DMSO-d_6			1·30(s)	1·60–2·40(m)
p		H	Ph	DMSO-d_6			1·05(s)	1·8–2·60(m)
q	OEt	H	Ph	$CDCl_3$	2·33(s)	2·56(s)	1·80(s)	1·9–2·6(m)
r	*m*-$NO_2C_6H_4$	H	*p*-$NO_2C_6H_4$	DMSO-d_6			1·68(s)	1·60(d) and 1·80(d)
s	*p*-ClC_6H_4	H	*p*-$NO_2C_6H_4$	$CDCl_3$			1·63(s)	1·60(d) and 1·85(d)
t	OEt	H	*p*-$NO_2C_6H_4$	CD_3NO_2	2·12(s)	1·60(d) and 2·20(d)	1·73(s)	1·60(d) and 1·82(d)

† The NMR spectra were recorded with a Varian A-60 spectrometer using TMS as an internal standard. The absorptions are given in τ-values and the multiplicity is indicated as follows: s = singlet. d = doublet. q = quartet. m = two multiplets.

from eq. 1 with the other two regioisomers from eq. 2 further establishes the position of the carbethoxy group in this particular case.



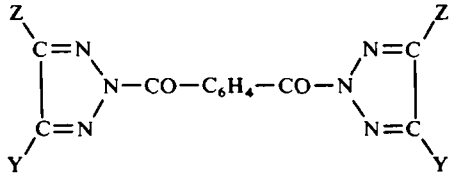
(4) The doublets corresponding to the *ortho* protons (with respect to the triazole nucleus) of the *p*-nitrophenyl substituent in **4r–t** at τ1·8 are deshielded by about 0·4 ppm compared with the corresponding doublets in **3**. The deshielding effect is of the same magnitude as the shift observed for the *ortho* protons in **4i–q**, and is due to the presence of a coplanar electron-withdrawing triazole ring. Similarly, the triazole protons in **4n, q, t** (at τ1·7–1·8) experience a large downfield shift relative to the triazole protons in **3n, q, t** (at τ2·1–2·3), as expected for different dihedral angles between the two aromatic planes.

In addition to the NMR criteria discussed above, the following convenient experimental test can be used for regiochemical assignments. The NMR spectrum of the triazole is recorded before and after addition of a base such as triethylamine or 1,4-diazabicyclo[2.2.2]octane. If no change is observed, the triazole had structure **4**. In our experiments all triazoles of structure **3** have isomerized to **4** and, hence, produced different absorptions when treated with these bases.

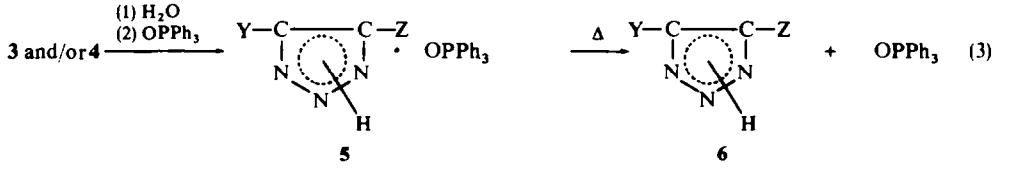
Prior to our work in this field, Harvey[2] obtained triazole **4m** by eq. 1 but assigned to it structure **3m**. Since no spectral or chemical evidence was advanced to elucidate its regiostructure, we have repeated this experiment and characterized both triazoles **3m** and **4m** by NMR. When the reaction of benzoylmethylenetriphenylphosphorane (**1**, Y = H, Z = Ph) and 3,4-dichlorobenzoyl azide was followed by NMR, the spectra showed the successive appearance and disappearance of a sharp peak at τ2·57 which we attribute to the phenyl group in the 5-position of **3m**. Its maximum intensity occurred after about 1 hr. The triazole isolated in 80% yield after complete reaction shows two multiplet absorptions (at τ2·0–2·2 and 2·4–2·6) for the phenyl group, compatible with structure **4m**.

Zbiral and Stroh[9] also studied the title reaction and reported the formation of the three possible regioisomeric triazoles. The authors, however, concluded that thermal isomerization must have occurred during their work-up procedure since the triazoles were isolated by distillation.

From Table 1 it is apparent that eq. 1 provides a general method for the synthesis of N-2 acyl and N-2 carbethoxy-1,2,3-triazoles (**4**). In particular, the reactions of **1** with terephthaloyl azide and isophthaloyl azide furnish bistriazoles (Table 1, cases **4h**, **4o** and **4p**) of the following type:



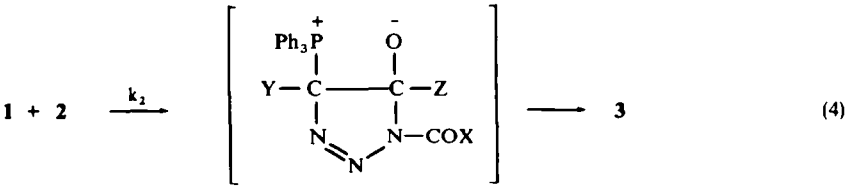
In the synthetic procedure we have used solvents p. a. without further purification. Since N-acyltriazoles are very susceptible to hydrolysis.[10] the rather low yields in some cases can be improved by working with well-dried solvents. For instance, when the solvent. CH_2Cl_2, was dried over molecular sieves. type 4A. the yield of triazole **4s** rose from 29 to 92%. In addition, we have observed side doublets (*ca* 7%) at τ7·70 (J = 0·5 Hz) in the NMR spectra of the reactions leading to **4c** and **4g**. When D_2O was added to a finished reaction leading to **4c**. the Me peak at τ7·50 decreased in favor of the doublet at τ7·70. The latter absorption does not correspond to the pure hydrolyzed triazole **6c**. which resonates 7 cps at lower field. but to its 1 : 1 complex with triphenylphosphine oxide (**5c**) (eq. 3). We have isolated such a complex in one case. namely from the reaction of *p*-nitrobenzoylmethylenetriphenylphosphorane (**1**. Y = H. Z = *p*-$NO_2C_6H_4$) with *m*-nitrobenzoyl azide. where **5r** was isolated in 80% yield. This complex decomposed to **6r** when refluxed in C_6H_6.*



5 6

Kinetics

In a previous publication on the reactions of aryl azides with α-keto phosphorus ylides. we reported that the kinetic results were best interpreted by assuming a highly developed enolate character in the ylide structure.[3] In the meantime. this proposal has been confirmed unambiguously by NMR.[1] Furthermore, Zeliger, *et al.*[1a] have clearly demonstrated by variable temperature NMR spectra that the α-keto phosphorus ylides of the type used in this work exist exclusively in the *cis*-configuration (**1**).† Consequently. the cycloaddition step in eq. 1. leading to the intermediate **7**. is expected to proceed by a concerted mechanism in the same way as described by Huisgen[12] for 1.3-dipolar additions to olefins and supported by orbital symmetry considerations.[13]



7

* The position of the N-H hydrogen atom in the N-unsubstituted triazoles has been the subject of current contradictory discussions.[6,11]

† Whether the term configuration or conformation should be used here is open to discussion; see IUPAC *Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry J. Org. Chem.* **35**. 2849 (1970)

Experimental evidence is provided by the low activation entropies reported in Table 3 for three typical examples. Conclusions regarding the nature of the transition-state have already been drawn.[3, 14] and the data of Table 3 further confirm them.

TABLE 3. RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE REACTIONS OF 1 WITH *m*-$NO_2C_6H_4CO$-N_3 IN BENZENE

Ylide 1	Temp	$10^3 k_2$ sec^{-1} 1 $mole^{-1}$	$\Delta E^‡$ kcal $mole^{-1}$	$\Delta S^‡$ (at 25°) e.u.
Y = H. Z = Me	5·0	3·57	12·0	−29
	19·0	10·25		
	25·0	14·8		
	30·0	21·2		
Y = H. Z = Ph	5·5	0·54	12·7	−30
	25·6	2·5		
	33·2	4·05		
	40·0	6·7		
Y = H. Z = *p*-$NO_2C_6H_4$	25·0	0·14	14·2	−30·4
	30·0	0·22		
	40·0	0·45		
	45·0	0·61		
	50·0	0·90		

TABLE 4. REACTION CONDITIONS LEADING TO THE ISOLATION OF **3n, t** AND **4n, t**

Triazole. %	Reaction conditions solvent. time. temp	% azide left by IR
3n. 63%	CH_2Cl_2. 9 days. 20°	10%
4n. 75%	CH_2Cl_2. 15 days. 20°	0%
3n. 75%	CH_2Cl_2. 3 days. 36°	13%
4n. 60%	C_6H_6. 8 days. 36°	0%
3n. 81%	DMF. 7 days. 20°	2%
4n. 69%	DMF. 10 days. 20°	0%
4n. 81%	DMSO. 8 days. 20°	0%
3t. 70%	CH_2Cl_2. 1 day. 20°	20%
4t. 76%	CH_2Cl_2. 14 days. 20°	0%
4t. 88%	C_6H_6. 1 day. 50°	0%
3t. 58%	DMF. 3/4 day. 20°	5%
4t. 65%	DMF. 14 days. 20°	0%
3t. 62%	DMSO. 3/4 day. 20°	12%

EXPERIMENTAL

General procedure for the synthesis of **4**. Equimolar amounts (0·02 mole) of ylide **1** and azide **2** were reacted in 100 ml of CH_2Cl_2 or C_6H_6 at room temp to completion (checked by IR). Triazole **4o** precipitated spontaneously from the CH_2Cl_2 soln. To isolate the other triazoles. the solvent was removed and the residue crystallized from MeOH (**4a, c, d, e, f, j, k, l, m, n, q, s, t**) or fractionally crystallized from ether (**4b, g, i**) or C_6H_6 (**4h, p, r**). The yields. recrystallization solvents and m.p. of the triazoles are given in

Table 1. Their C. H and N analyses were within 0·3%. The compounds **4b–t** displayed the typical =C—H stretching vibrations at 3100–3130 cm^{-1} in the IR spectra (KBr).

Isolation of triazoles of structure **3**. In order to isolate **3n** and **3t**. experiments were carried out under a variety of conditions and the reactions worked up prior to completion. The course of the reaction was easily followed by IR using the azide stretching absorption at about 2130 cm^{-1}. The results are recorded in Table 4 (for clarity. the conditions which led to the isolation of **4n** and **4t** are also included).

Compounds **5r** *and* **6r**. When reaction of **1** (Y = H. Z = p-$NO_2C_6H_4$) with m-nitrobenzoyl azide was carried out in wet CH_2Cl_2. complex **5r** was isolated in 80% yield: m.p. 176·5–178°; NMR (DMSO-d_6): τ 1·69 (s. 1H. =C—H). 1·62 and 1·83 (2d. 4H. J = 9 Hz). The mass spectrum does not show a molecular ion peak of the complex. but fragmentation patterns of the two products triphenylphosphine oxide[15] and **6r**. m/e (%): 190 (42. $M^{\cdot+}$). 162 (16. $M^{\cdot+} - N_2$) and 89 (32. 162 —NO_2—HCN): (Calcd for $C_{26}H_{21}N_4O_3P$ (468): C. 66·66: H. 4·49: P. 6·62. Found: C. 66·55: H. 4·45: P. 6·55%). Decomposition of **5r** in refluxing C_6H_6 precipitated **6r**: m.p. 201–203° (lit.[2] 198–199°): NMR (DMSO-d_6): τ 1·42 (s. 1H. =C—H). 1·68 and 1·90 (2d. 4H. J = 9 Hz).

Kinetics. The kinetic results were obtained by reacting equimolar amounts of ylide and m-nitrobenzoyl azide in C_6H_6 at the appropriate temp. and recording the disappearance of the azide band at about 2140 cm^{-1} in the IR as a function of time. Details concerning the procedure have been described elsewhere.[3,14]

Acknowledgement—The authors are indebted to Dr. S. Toppet for her advice in the interpretation of the NMR spectra and to W. Spreutels for his excellent technical assistance. Thanks are due to the N.F.W.O. Belguim and to the I.R.S.I.A. Belgium for a postdoctoral (G.L'a) and doctoral (P.Y.) fellowship respectively. Financial support from the F.K.F.O. Belgium is gratefully acknowledged.

REFERENCES

[1] [a] H. I. Zeliger. J. P. Snyder and H. J. Bestmann. *Tetrahedron Lett.* 3313 (1970);
[b] J. P. Snyder and H. J. Bestmann. *Ibid.* 3317 (1970);
[c] I. F. Wilson and J. C. Tebby. *Ibid.* 3769 (1970);
[d] M. L. Filleux-Blanchard and G. J. Martin. *C.R. Acad. Sc. Paris* **270**. 1747 (1970)
[2] G. R. Harvey. *J. Org. Chem.* **31**. 1587 (1966)
[3] P. Ykman. G. L'abbé and G. Smets. *Tetrahedron* **27**. 845 (1971)
[4] A. Hassner. *J. Org. Chem.* **33**. 2684 (1968)
[5] P. Ykman. G. L'abbé and G. Smets. *Tetrahedron Lett.* 5225 (1970)
[6] L. Birkofer and P. Wegner. *Chem. Ber.* **99**. 2512 (1966) and **100**. 3485 (1967)
[7] L. M. Jackman and S. Sternhell. *Applications of NMR in organic chemistry*. Edited by D. H. R. Barton and W. Doering p. 201–214 and 331. Pergamon Press. London (1969)
[8] [a] G. Garcia-Muñoz. R. Madroñero. M. Rico and M. C. Saldaña. *J. Heterocycl. Chem.* **6**. 921 (1969);
[b] G. L'abbé and A. Hassner. *Bull. Soc. Chim. Belges* **80**. 209 (1971)
[9] E. Zbiral and J. Stroh. *Monatsh. Chem.* **100**. 1438 (1969)
[10] [a] R. Hüttel and J. Kratzer. *Chem. Ber.* **92**. 2014 (1959);
[b] H. A. Staab. *Angew. Chem.* **74**. 407 (1962)
[11] [a] E. Borello and A. Zecchina. *Ann. Chim.* (Rome) **52**. 1302 (1962); *Chem. Abstr.* **58**. 13751g (1963); E. Borello. A Zecchina and E. Guglielminotti. *J. Chem. Soc. (B)* 307 (1969);
[b] H. Gold. *Liebigs Ann. Chim.* **688**. 205 (1965);
[c] M. L. Roumestant. P. Viallefont. J. Elguero and R. Jacquier. *Tetrahedron Lett.* 495 (1969)
[12] R. Huisgen. *Angew. Chem.* **75**. 741 (1963); *Angew. Chem. Internat. Edit.* **2**. 633 (1963); *J. Org. Chem.* **33**. 2291 (1968)
[13] R. B. Woodward and R. Hoffmann. *Angew. Chem.* **81**. 797 (1969); *Angew. Chem. Internat. Edit.* **8**. 781 (1969)
[14] G. L'abbé. P. Ykman and G. Smets. *Tetrahedron* **25**. 5421 (1969)
[15] D. H. Williams. R S. Ward and R. G. Cooks. *J. Amer. Chem. Soc.* **90**. 966 (1968)