Reactions of Azides with Isocyanates. Cycloadditions and Cycloreversions

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Reactions of alkyl azides with aryl isocyanates, acyl isocyanates, carboalkoxy isocyanates, and sulfonyl isocyanates, as well as reactions of aryl azides with sulfonyl isocyanates, provide a convenient method for the synthesis of 1,4-disubstituted Δ^2 -tetrazolin-5-ones (5, 6, and 9). 1-Alkyl-4-sulfonyl- Δ^2 -tetrazolin-5-ones (9a-e) undergo cycloreversion upon thermolysis. The forward and reverse reactions are accelerated by the introduction of electron-withdrawing groups on the isocyanate molety. The kinetics of the cycloreversion reaction of selected examples were studied; energies of activation and heats of reaction were determined.

Only a few reactions of azides with isocyanates have been reported. The lack of interest in this topic probably originates from the recognition that alkyl and aryl isocyanates can be prepared from acyl azides by the well-known Curtius rearrangement,¹ and, hence, do not react with their precursors. Photochemically, however, aroyl azides yield aroylnitrenes,² which were shown by Lwowski³ to react with ethyl isocvanate to give 2-aryl-4-ethyl-1,3,4-oxadiazolin-5-ones (1). Ther-

$$EtN = C = O + p \cdot XC_{6}H_{4}CON_{3} \xrightarrow{h\nu} EtN \xrightarrow{C = O} \\ \downarrow \\ N \searrow_{C} O \\ \downarrow \\ p \cdot C_{6}H_{4}X \\ 1$$

molysis and photolysis of azidoformates in the presence of alkyl isocyanates also led to oxadiazolinones, but the major products in this case were 1-carboalkoxy-2,4dialkylurazoles (2). The intermediacy of 1-carboalkoxy-4-alkyl- Δ^2 -tetrazolin-5-ones (3) in this reaction might be postulated but is questionable.



A suitable synthetic route to monosubstituted Δ^2 tetrazolin-5-ones (4) is available and involves the reac-



tion of aluminum azide with aryl isocyanates in tetrahydrofuran.⁴ Sodium azide failed to react with isocyanates, while hydrazoic acid reacted in a different manner to give carbamoyl azides.⁵

1,4-Disubstituted Δ^2 -tetrazolin-5-ones, though synthesized on several occasions,⁶ were until now not accessible by a general and direct method. We now wish to report that several 1.4-disubstituted Δ^2 -tetrazolin-5-ones are readily prepared by 1,3-dipolar cycloaddition of alkyl azides, and to a lesser extent aryl azides, with suitable isocyanates. We also found that electronegatively substituted adducts undergo cycloreversion on thermolysis. The results are described in the present paper.

Additions to Arvl Isocvanates.-Butvl isocvanate was found to be unreactive toward all azides used, *i.e.*, butyl azide, phenyl azide, p-nitrophenyl azide, p-methoxyphenyl azide, and tosyl azide. No change in the ir spectra was observed when the reagents were mixed and allowed to stand for several months at 60°.

Although aryl isocyanates also did not react with aryl azides and tosyl azide, slow addition was observed with equimolar amounts of butyl azide and cyclohexyl azide. The reactions were monitored by ir (2200 and 2100 cm^{-1}) and the corresponding cycloadducts (5) were isolated in high yields (see Table I).



TABLE I Synthesis of 1-Alkyl-4-aryl- Δ^2 -tetrazolin-5-ones (5)

Compd	R	x	Solvent, temp in °C, time	Yield, %	Mp, °C
5a	n-C ₄ H ₉	H	130, 23 days	80	Liquid, bp 132 (0.7 mm)
5b	n-C ₄ H ₉	NO_2	C_6H_{6} , ^{<i>a</i>} reflux, 40 hr	72	86.5-87
5с « Сал	c-C ₆ H ₁₁ ried out	NO_2 in 1 M :	55, 10 days solution.	86	192 - 195

⁽⁴⁾ J. P. Horwitz, B. E. Fisher, and A. J. Tomasewski, J. Amer. Chem. Soc., 81, 3076 (1959).

P. A. S. Smith, Org. React., 3, 337 (1946).
 L. Horner and A. Christmann, Chem. Ber., 96, 388 (1963); L. Horner, G. Bauer, and J. Dörges, ibid., 98, 2631 (1965).

⁽³⁾ W. Lwowski, Trans. N. Y. Acad. Sci., 33, 259 (1971).

⁽⁵⁾ E. Lieber, R. L. Minnis, and C. N. R. Rao, Chem. Rev., 65, 377 (1965).

^{(6) (}a) K. Hattori, E. Lieber, and J. P. Horwitz, J. Amer. Chem. Soc., **78**, 411 (1956); (b) D. F. Percival and R. M. Herbst, J. Org. Chem., **22**, 925 (1957); (c) J. K. Elwood and J. W. Gates, *ibid.*, **32**, 2956 (1967); (d) W. S. Wadsworth, ibid., 34, 2994 (1969); (e) R. Raap and J. Howard, Can. J. Chem., 47, 813 (1969).

Characterization of the products followed from spectral and microanalysis. In particular, the ir spectra exhibited the expected^{4,6} strong C=O absorptions at 1725-1735 cm⁻¹ (absence of electron delocalization).

Chemically, compounds of type 5 were thermally stable and inert toward acids as previously reported.⁶ Thus, heating a sample of 5a at 250° for several hours did not induce decomposition. It must be pointed out that a concerted thermal supra-supra elimination of nitrogen from 5 is symmetry forbidden.⁷

Additions to Acyl and Carboalkoxy Isocyanates. Efforts to obtain cycloadducts from the reactions of aryl azides with benzoyl isocyanate, chloroacetyl isocyanate, and trichloroacetyl isocyanate (few months at 60°) were unsuccessful. On the contrary, when isocyanates were treated with alkyl azides in the absence of solvent, 1-alkyl-4-acyl (or carboalkoxy) Δ^2 -tetrazolin-5-ones (6) were obtained in good yields. Table II lists



Table II Synthesis of 1-Alkyl-4-acyl (or carboalkoxy) Δ^2 -Tetrazolin-5-ones (6)

Compd	R	R'	°C	Time, days	Yield, %	Mp, °C
ба	$n-C_4H_9$	C_6H_5	25	30	0	
	-	-	100	7	> 80	Oil
бb		$p-\mathrm{NO}_2\mathrm{C}_6\mathrm{H}_4$	55	13	65	79-81.5
бс		ClCH ₂	25	2	0	
			55	6	$>\!80$	a
6 d		$Cl_{a}C$	25	6	> 80	Oil
бе		OC_2H_5	55	30	>80	Oil
6f		OC_6H_5	55	30	>80	Oil
бg	$i-C_{3}H_{7}$	$ClCH_2$	55	8	70	104 - 107
6h		Cl_3C	25	10	$>\!80$	a
6i		$OC_{6}H_{5}$	55	25	82	120-124.5
6j	c-C ₅ H ₉	C_6H_5	100	11	73	56 - 58
6k	c-C ₆ H ₁₁	C_6H_5	100	7	82	96-99
61		$ClCH_2$	55	8	75	113 - 125
бm		Cl_3C	25	6	$>\!80$	a
6 n		OC_6H_5	55	25	87	111 - 113

 a Hygroscopic solids which hydrolyze in contact with atmosphere.

the results and also illustrates the rate enhancement by the introduction of electron-withdrawing substituents on the isocyanate.

The structures 6a-n were ascertained by spectral analyses. Worth mentioning are the typical ir absorptions at 1770–1810 and at 1720–1730 cm⁻¹ corresponding respectively to the side chain C=O⁸ and ring C=O stretching vibrations.

To test thermal stability, one selected example (6n) was heated in nitrobenzene at 150° for 3 days and recovered in almost quantitative yield. The ir spectrum of the crude product, however, showed the presence of

a small amount of azide (2100 cm^{-1}), resulting from cycloreversion.

The new compounds of type 6 all exhibited the unusual properties attributed to azolides.⁸ For instance, they underwent facile hydrolysis and alcoholysis at room temperature to yield 1-alkyl- Δ^2 -tetrazolin-5-ones (7). In some cases, hydrolysis even occurred with



atmospheric moisture, preventing the isolation of the adducts in the pure state (see Table II). We made use of this property to prepare bistetrazolinone 8 by



reaction of 1,5-diazidopentane with trichloroacetyl isocyanate and subsequent methanolysis of the crude mixture. Compound **8** was isolated in 65% overall yield. The existence of **7** and **8** in the keto form rather than in the tautomeric hydroxytetrazole form has been established previously.^{4,6a,9}

Additions to Sulfonyl Isocyanates.—Sulfonyl isocyanates were found to react readily with alkyl and aryl azides to give 1-alkyl (or aryl) 4-sulfonyl- Δ^2 -tetrazolin-5-ones (9) in good yields (see Table III). Bistetrazo-



linones were also prepared by this method from diisocyanates or diazides. Thus, 9j was obtained from *m*-phenylenedisulfonyl isocyanate and *n*-butyl azide (55°, 3 days), and 9k resulted from the interaction of *p*-tolylsulfonyl isocyanate and 1,5-diazidopentane (55°, 6 days).



(9) J. C. Kauer and W. A. Sheppard, J. Org. Chem., 32, 3580 (1967).

⁽⁷⁾ R. B. Woodward and R. Hoffman, Angew. Chem., **81**, 797 (1969); Angew. Chem., Int. Ed. Engl., **8**, 781 (1969). Photochemically induced elimination of nitrogen from 1,4-dimethyl- Δ^2 -tetrazolin-5-one has been reported; see ref 6d.

⁽⁸⁾ H. A. Staab, Angew. Chem., 74, 407 (1962); Angew. Chem., Int. Ed. Engl., 1, 351 (1962).

	N111.	CITEDOLO OL TITETTE (O	I INICIAL A COLL	U			
Compd	R	R'	Solvent	°C	Time, days	Yield, %	Мр, °С
9a	$n-C_4H_9$	p-CH ₃ C ₆ H ₄		55	6	70	51 - 52.5
		•	Toluenea	25	60	79	
9b		C_6H_5		55	5	82	42.5 - 43.5
			CCl_{4}^{b}	25	30	85	
9c		p-ClC ₆ H ₄	Toluenea	25	30	84	76-77.5
9d		p-NO ₂ C ₆ H ₄	$Toluene^a$	25	17	75	124 - 125
9e		$m-NO_2C_6H_4$	Toluene ^a	25	22	75	90-91
9f		Cl	C_6H_6	25	Instan-	± 95	с
					taneous		
9g	C_6H_5	$p-\mathrm{ClC_6H_4}$		55	90	± 60	177.5 - 178
9h	p-CH ₃ C ₆ H ₄	$p-\mathrm{ClC_6H_4}$		87	7	35	195.5 - 196.5
9i	p-CH ₃ OC ₆ H ₄	$p-ClC_6H_4$		55	30	70	183.5 - 184
^a Carried	out in $0.6 M$ solution.	^b Carried out in 1.5	\dot{M} solution. \circ (Colorless, hy	groscopic liqui	d, bp 60-70° (2 mm), ir 1765 cm ⁻¹ .

TABLE III Synthesis of 1-Alkyl (or Aryl) 4-Sulfonyl-Δ²-tetrazolin-5-ones (9)

TABLE IV

Kinetics of Cycloreversion of 1-n-Butyl-4-sulfonyl- Δ^2 -tetrazolin-5-ones in Chlorobenzene (0.05 mol $1.^{-1}$)

		$10^{4}k_{1}$	min -1					
	Temp,	C=0	N 3	ΔE^{\pm} , ke	$\frown \Delta E^{\pm}$, kcal mol ⁻¹		ΔS [‡] at 114.8°, eu	
Compd	°C	method	method	C=0	N_3	C=0	N 3	
9a	100.8	1.1	1.4	33.6	29.3	2.9	-0.3	
	114.8	6.6	5.9					
	124.8	18.0	15.7					
9b	100.8	1.6	2.0	33.2	31.6	2.5	6.7	
	114.8	9.0	10.1					
	124.8	26.4	29.0					
9c	100.8	4.0	4.1	32.7	30.2	3.1	4.5	
	114.8	23.0	20.3					
	124.8	63.1	47.4					
9d	92.0	7.7		30.4		2.3		
	100.8	22.3	16.1					
	114.8	91.0	87.5					
9e	92.0	8.4		30.0		-0.9		
	100.8	26.9	23.3					
	114.8	103.0	98.6					

Compounds 9a-k exhibited strong ir (KBr) absorptions near 1750 cm⁻¹. As expected,⁸ they were more resistant than 6 toward nucleophilic attack by water and alcohol. For instance, ethanolysis of 9c only occurred after being held more than 2 days at reflux temperature. An exception to this general behavior was provided by compound 9f, which decomposed in contact with the atmosphere to give an unidentified viscous material.

Cycloreversions of 1-Alkyl-4-sulfonyl- Δ^2 -tetrazolin-5-ones.—Although retro Diels-Alder reactions are well known,¹⁰ only a few cycloreversions of 1,3-dipole adducts have been reported.¹¹ No examples are known in the azide field.¹² We have now found that 1-alkyl-4-sulfonyl- Δ^2 -tetrazolin-5-ones (9) undergo thermal decomposition at about 100° into starting materials. The reactions gave equilibrium compositions, for which the rates of cycloreversion and cycloaddition were equal. Kinetic measurements were carried out with typical examples (9a-e) in chlorobenzene solution using ir

(12) R. Huisgen [Angew. Chem., Int. Ed. Engl., 2, 570 (1963)] reported briefly the formation of methyl azide and benzonitrile upon thermolysis of 2-methyl-5-phenyltetrazole. The reaction, however, was not reversible. techniques. The reaction rates were determined both by recording the decrease of the tetrazolinone C==O absorption (1750 cm⁻¹) and the progressive formation of the azide absorption (2100 cm⁻¹). Good agreement was obtained between the two methods. The initial first-order rate constants (k_1) and activation parameters are given in Table IV.

A linear Hammett correlation was observed with a ρ value of +1.4 at 114.8°. Thus, the rate of cycloreversion increased with increasing electronegativity of the isocyanate moiety, as was also observed for the forward reaction. The activation entropies of the cycloreversions are low compared with values reported for ring opening of substituted 5-aminotetrazoles,¹³ and, hence, are not consistent with an open-chain betaine intermediate. The influence of solvent polarity on the rate of cycloreversion also points to the same conclusion. Thus, the decomposition rate constants for **9b** in chlorobenzene and nitrobenzene at 125° were 26.4×10^{-4} and 70×10^{-4} min⁻¹, respectively. The observed increase is too low to account for a betaine intermediate.¹⁴

All the results thus far obtained on the cycloaddition and cycloreversion reactions are compatible with a

⁽¹⁰⁾ H. Kwart and K. King, Chem. Rev., 68, 415 (1968).

⁽¹¹⁾ A. Mustafa, J. Chem. Soc., 234 (1949); G. K. Buckley, *ibid.*, 1850 (1954); R. Grashey and K. Adelsberger, Angew. Chem., 74, 292 (1962); Angew. Chem., Int. Ed. Engl., 1, 267 (1962); R. Grashey, H. Leitermann, R. Schmidt, and K. Adelsberger, Angew. Chem., 74, 491 (1962); Angew. Chem., 1nt. Ed. Engl., 1, 406 (1962); R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, Chem. Ber., 101, 2568 (1968); 102, 736 (1969).
(12) R. Huisgen [Angew. Chem., Int. Ed. Engl., 2, 570 (1963)] reported

⁽¹³⁾ R. A. Henry, W. G. Finnegan, and E. Lieber, J. Amer. Chem Soc., 77, 2264 (1955).

⁽¹⁴⁾ R. Huisgen, Angew. Chem., 75, 741 (1963); Angew. Chem., Int. Ed. Engl., 2, 633 (1963); J. Org. Chem., 33, 2291 (1968).

concerted mechanism, involving a charge imbalance in the transition state as shown in 10.



Since the systems give equilibrium mixtures, the equilibrium constants at different temperatures were determined and the heats of reaction were calculated (see Table V). The cycloreversions were endothermic

TABLE V EFFECT OF TEMPERATURE ON EQUILIBRIUM CONSTANTS

$K_{eq} = [azide][isocyanate]/[adduct]$

	K_{eq} , mol l1 Hea						
	Temp,	C=0	N_3	reaction,			
Compd	°C	method	method	kcal mol-1			
9a	101.0	3.6	4.4	18.1			
	107.7	6.2	5.9				
	114.7	7.8	7.4				
	124.5	15.9	15.7				
9c	101.3	4.1	4,4	15.9			
	107.7	7.0	7.1				
	114.7	9.3	8.9				
	124.2	15.3	15.8				
9e	101.0	4.6	5.1	10.8			
	107.5	7.0	6.0				
	115.5	9.4	8.6				
	119.7	9.6	10.1				

for 10-18 kcal mol⁻¹. From the activation energies of the cycloreversion and the heats of reaction, a rough estimation of the activation energies of the cycloaddition process can be made. The values thus obtained (13–19 kcal mol⁻¹) are in good agreement with those published for reactions of azides with dipolarophiles.¹⁵

Finally a concluding remark concerning the reaction leading to compound 2 is in order. At least thermally, compound 3 cannot be an intermediate for two reasons. First, alkyl isocyanates do not react at all with azides. Second, compounds of type 3 do not eliminate nitrogen on thermolysis but, instead, were shown to cycloreverse slowly. The mechanism of the reaction remains obscure.

Experimental Section

Aryl isocyanates,¹⁶ acyl isocyanates,¹⁷ and sulfonyl isocyanates¹⁸ were prepared as reported.

General Procedure for the Synthesis of 1,4-Disubstituted Δ^2 -Tetrazolin-5-ones (5, 6, and 9).—Equimolar amounts of azide and isocyanate were allowed to react in the absence of solvent, unless otherwise stated (see Tables I-III). In the case of 6b an excess of azide was used. After complete reaction (monitored by ir), the adducts were isolated by crystallization from ether (solids) or by distillation under reduced pressure (liquids). The solids were recrystallized from ether, except 9k, which was recrystallized from acetone. The products were characterized by ir (KBr or neat), nmr, and microanalysis. The C, H, N, and O analyses of the water-stable adducts were within 0.3%.

Acid Treatment of Tetrazolinones 5a and 5b .--- Compound 5a (1 g) was heated in HCl solution (20 ml, 10 N) at 60° for 24 hr.

(16) G. Labbe, Chem. Rev., 69, 345 (1969).
(16) R. L. Shriner, W. H. Horne, and R. F. B. Cox, "Organic Syntheses,"
Collect. Vol. II, Wiley, New York, N. Y., 1946, p 453.
(17) A. J. Speziale and L. R. Smith, J. Org. Chem., 28, 1805 (1963);
A. J. Speziale, L. R. Smith, and J. E. Fedder, *ibid.*, 30, 4306 (1965).

(18) H. Ulrich, B. Tucker, and A. A. R. Sayigh, ibid., 31, 2658 (1966).

The mixture was then neutralized with NaOH and extracted with ether to regenerate 5a in quantitative yield.

Compound 5b (2.5 g) was heated in concentrated H₂SO₄ solution (15 ml) for 24 hr. The mixture was poured into ice and **5b** was recovered in nearly quantitative yield.

Hydrolysis and Methanolysis of 6.-Compounds of type 6 hydrolyzed or methanolyzed instantaneously in contact with water or methanol. The ir absorption bands at 1770-1810 cm $^{-1}$ disappeared in favor of bands in the region 1680–1750 cm $^{-1}.$ The following products were isolated in the pure state: 7 (R = $c-C_6H_{11}$), 75%, mp 122-123° (toluene); 7 (R = $c-C_5H_9$), 79% mp 134-135°; 8, 65%, mp 164-166° (MeOH).

Thermolysis of 9c.-Compound 9c was heated at 130° in a distillation flask. Butyl azide was distilled off and characterized by comparison with an authentic sample. The residue was shown to contain p-chlorobenzenesulfonyl isocyanate, ir 2200 cm⁻¹.

Kinetics .-- Pure tetrazolinone was accurately weighed and dissolved in dry solvent. The solution was maintained at constant temperature, and the reaction was followed spectrometrically (Perkin-Elmer ir 521 instrument) using the intensity of the tetrazolinone C=O and azide N₃ absorption bands. The concentrations were determined from the observed absorptions using calibration curves. Measurements were made within the first 20% conversion. The first-order rate constants were determined from the slopes of log (C=O or N_3) vs time. The energies of activation were determined from the Arrhenius plots of log k_1 vs. 1/T. The entropies of activation were calculated from the rate constants at 114.8° by use of the Eyring equation: $\Delta S^{\pm} = 4.576 \log k_1 (\sec^{-1}) - 49.14 - 4.576 \log T + \Delta E^{\pm}/T.$

Determination of Equilibrium Constants.—The constants K_{eq} were determined under strictly anhydrous conditions, using highvacuum techniques. Sealed samples of tetrazolinone in chloro-benzene were allowed to equilibrate at the appropriate temperature. Product concentrations were then determined by ir. Heats of reaction were calculated from the curves of log K_{eq} vs. 1/T. (Decomposition of the azide under the equilibrium conditions occurred to a small extent. Thus, when butyl azide was heated in chlorobenzene at 115° for 5 days, 10% decomposition was observed.)

Registry No. -5a, 37495-05-9; 5b, 37495-06-0; 5c, 37495-07-1; 6a, 37495-08-2; 6b, 37528-57-7; 6c, 37495-09-3; 6d, 37495-10-6; 6e, 37495-11-7; 6f, 37495-12-8; **6g**, 37495-13-9; **6h**, 37495-14-0; **6i**, 37495-15-1; 6j, 37495-16-2; 6k, 37495-17-3; 6l, 37495-18-4; 6m, 37495-19-5; 6n, 37528-58-8; 7 (R = $c-C_6H_{11}$), 37495-20-8; 7 (R = c-C₅H₉), 37495-21-9; 8, 37495-22-0; 9a, 37495-23-1; 9b, 37495-24-2; 9c, 37495-25-3; 9d, 37666-05-0; 9e, 37528-59-9; 9f, 37495-26-4; 9g, 37642-67-4; 9h, 37495-27-5; 9i, 37495-28-6; 9j, 37495-29-7; 9k, 37495-30-0; RN_3 ($R = n-C_4H_9$), 7332-00-5; RN_3 (R = $c-C_{6}H_{11}$), 19573-22-9; RN₃ (R = $i-C_{3}H_{7}$), 691-57-6; RN_3 (R = c-C₅H₉), 33670-50-7; RN_3 (R = C₆H₅), 622-37-7; RN_3 (R = $p-CH_3C_6H_4$), 2101-86-2; RN_3 $p-NO_2C_6H_4$), 4461-37-4; R'CONCO (R' = ClCH₂), 4461-30-7; R'CONCO ($R' = Cl_3C$), 3019-71-4; R'-CONCO ($R' = OC_2H_5$), 19617-43-7; R'CONCO (R' = OC_6H_5), 5843-43-6; R'SO₂NCO (R' = p-ClC₆H₄), 5769-15-3; R'SO₂NCO (R' = p-CH₃C₆H₄), 4083-64-1; $R'SO_2NCO (R' = C_6H_5), 2845-62-7; R'SO_2NCO (R' = p-NO_2C_6H_4), 5769-16-4; R'SO_2NCO (R' = m-NO_2 C_6H_4$), 7018-79-3; R'SO₂NCO (R' = Cl), 1189-71-5; 1,5-diazidopentane, 17607-21-5; *m*-phenylenedisulfonylisocyanate, 3611-91-4.

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⁽¹⁵⁾ G. L'abbé, Chem. Rev., 69, 345 (1969).