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TRIAZOLINES—II

SOLVENT EFFECTS ON THE 1,3-CYCLOADDITION OF DIAZOMETHANE TO SCHIFF BASES AND THE SYNTHESIS OF 1,5-DIARYL-1,2,3-TRIAZOLINES[1]

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Abstract—Second order rate constants for the 1,3-cycloaddition of diazomethane to benzalanilines (Schiff bases) have been determined. The results do not reveal any general dependence of rate on the dielectric constant of the solvents; there is, however, a definite acceleration in the presence of associated solvents such as water. The kinetic data are discussed and a concerted mechanism postulated for the addition reaction. The significant effect of water on the reaction rate has led to a versatile method for the synthesis of 1,5-diaryl-1,2,3-triazolines in good yields, by the cycloaddition of diazomethane to Schiff bases in aqueous dioxane solutions. Earlier attempts by other workers to react diazomethane with Schiff bases in dry ethereal solutions or in the presence of methanol as catalyst has been largely unsuccessful or has yielded only insignificant amounts of the adduct. At the present time, the cycloaddition in aqueous dioxane solutions appears to be the only general method of synthesis for the 1,5-diaryl-1,2,3-triazolines.

THE addition of diazoalkanes to activated olefinic double bonds is a well known route to the synthesis of pyrazolines.[3] The addition of diazomethane in a similar manner to carbon–nitrogen double bonds bearing active groups, may be expected to lead to a general method for the synthesis of the Δ^2-1,2,3-triazolines. Mustafa[4] observed the formation in small quantities of a stable addition product by the action of diazomethane on aromatic anils (Schiff bases) in a few instances, and Buckley[5] showed these to have a 1,2,3-triazoline structure by comparison with the products obtained by the known addition of phenyl azide to olefins.[6] However, aside from these two papers, which list the formation of a total of six triazolines, this addition reaction has received little attention, in striking contrast to the extensive study on the addition of diazomethane to olefins to yield pyrazolines.

The addition reaction of diazomethane and Schiff bases falls within the type of additions, termed the "1,3-dipolar cycloadditions", by Huisgen and associates.[7] Kadaba and Edwards[1] investigated the kinetics of the addition, and postulated a two-step addition mechanism, a nucleophilic attack by the diazomethane carbon on the

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[1] P. K. Kadaba and J. O. Edwards, *J. Org. Chem.* **26**, 2331 (1961), is Part I in this series.

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[3] Summary in R. C. Elderfield, *Heterocyclic Chemistry* Vol. 5. Wiley, New York, N.Y., (1957); H. Zollinger, *Azo and Diazo Chemistry*. Interscience, New York, N.Y. (1961).

[4] A. Mustafa, *J. Chem. Soc.* 234 (1949).

[5] G. D. Buckley, *J. Chem. Soc.* 1850 (1954).

[6] L. Wolff, *Liebigs. Ann.* **394**, 23, 59, 68 (1912); **399**, 274 (1913); K. Alder and G. Stein, *Ibid.* **485**, 211 (1931); **501**, 1 (1933).

[7] R. Huisgen, *Angew. Chem.* (International Edn.) **2**, 565 (1963); **2**, 633 (1963).

double bond carbon of the anil (which is β- to the activating group, the N-phenyl group) with formation of a zwitterion intermediate (I), which is followed by rapid ring closure. Consistent with this mechanism, the rate of reaction was decreased by placing electron releasing groups on the benzene rings of the anil and enhanced by the presence of electron withdrawing groups, especially on the N-phenyl and striking results were observed where conjugated systems are possible.

Huisgen,[7] however, has proposed a one step concerted mechanism for the 1,3-cycloadditions in general, though the extent of simultaneity of bond formation is not completely known. There is little or no increase in reaction rate with solvents of rising dielectric constant (which is a measure of solvent polarity);[8] if a discrete dipolar intermediate were formed, a strong enhancement of rate with solvent polarity would be anticipated.[9]

Rate constants for the addition of diazomethane to benzalanilines in solvents of different dielectric constants have now been determined and the results have led to a versatile method for the synthesis of a variety of 1,2,3-triazolines.

EXPERIMENTAL[10]

Preparation of schiff bases. The Schiff bases were synthesized by known methods. Equimolar quantities of the appropriate aldehydes and amines were condensed, directly by warming the mixture when in the form of liquids, or by refluxing for 0·5–1 hr in the presence of a suitable solvent such as EtOH. *p*-Nitrobenzal-*p*-nitroaniline was prepared by refluxing in glacial AcOH.

In the case of benzal-*m*-nitroaniline, the mixture of aldehyde (in excess) and aniline was heated to 110–115° for 1 hr in an open round bottom flask, and the water formed was removed intermittently by applying reduced press. The resulting melt was repeatedly shaken with diethyl ether when the excess benzaldehyde was removed and the anil crystallized out in quite pure form.

All the anils were obtained in high yields and were purified by distillation under reduced press. or by crystallization from EtOH or acetone. Benzal-*m*-nitroaniline decomposed slightly during crystallization and an orange coloured product was formed which lowered the m.p. of the anil. *o*-Chlorobenzalaniline decomposed extensively when distilled. These were used without purification for triazoline synthesis and were found quite satisfactory.

Rate measurements. Rate constants for the addition of diazomethane to benzalaniline, benzal-*p*-chloroaniline and benzal-*p*-toluidine in various solvents were determined by the pseudo-first-order technique described earlier.[1] The anils were crystallized from appropriate solvents and air dried, or distilled under reduced press. The solvents used for the kinetic runs were all, of reagent grade quality. As the anil and diazomethane were both insoluble in water, the effect of this solvent was studied using dimethylformamide solutions of the anils containing 10% water. Instead of pure water, a very dilute solution of KOH was employed, as the diazomethane was found to be more stable under these conditions. The possibility of catalysis by hydroxide ions was eliminated, as the rate was not dependent on hydroxide ion concentration. The results are summarized in Table 1.

Synthesis of 1,2,3-*triazolines*

General method. In a typical experiment, the anil (0·015 mole) was dissolved with cooling, if necessary, in a freshly prepared solution of diazomethane (0·05 mole) in aqueous dioxan (75 ml) contained in an Erlenmeyer flask. The reaction mixture was then allowed to stand at R.T. for 2–4 days in the flask stoppered with a cork. Anils that reacted sluggishly were allowed to stand for 6–7 days. At the end of this period, the mixture was filtered, cooled and diluted with cold water (about

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[8] R. Huisgen, H. Stangl, H. J. Sturm and H. Wagenhofer, *Angew. Chem.* **73**, 170 (1961).

[9] N. Menschutkin, *Z. physik. Chem.* **6**, 41 (1890); H. G. Grimm, H. Ruf and H. Wolff, *Ibid.* **B13**, 301 (1931).

[10] M.ps were determined using an electrically stirred silicone oil bath. M.ps and b.ps are uncorrected. Microanalyses are by Dr. Kurt Eder, Laboratoire Microchimique, Ecole de Chimie, Geneve, Switzerland, and all nitrogen analyses are by Dumas method.

TABLE 1. RATE CONSTANTS FOR THE ADDITION OF DIAZOMETHANE TO BENZALANILINES IN VARIOUS SOLVENTS AT 24·9°

Solvent	Dielectric Constant[a]	$k_2 \times 10^3$, l . mole^{-1} hr^{-1}			
		Benzal Aniline	Benzal-*p*-Chloro-aniline	Benzal-*p*-toluidine	Benzal-*m*-Chloro-aniline
Cyclohexane	2·07	—	4·3	—	—
Dioxan	2·25	3·5[b]	5·2	1·2[b]	—
Benzene	2·28	—	5·8	—	—
Acetone	21·20	2·6	3·3	—	—
Dimethylformamide	37·60	2·0	7·9	1·8	12·5
Dimethylformamide +15% water[c]	—	—	16·4	—	—
Dimethylformamide +10% 0·04 N KOH	—	—	18·3	—	21·9
Dimethylformamide +10% 0·02 N KOH	—		—	—	22·1

[a] A. A. Maryott and F. Buckley, National Bureau of Standards Circular No. 589, U.S. Government Printing Office, Washington, D.C., 1958.

[b] Ref. 1.

[c] Dielectric constant of water at 20°, 80·4.

50–75 ml) with shaking until a permanent precipitation appeared. Further cooling in ice for 2–3 hr or in the refrigerator overnight, yielded the 1,2,3-triazoline as a fine crystalline material.

The diazomethane was prepared from nitrosomethylurea in the same manner undistilled ethereal solutions are obtained,[11] using 1,4-dioxan (Fisher Laboratory grade) in place of Et_2O. The temp was kept at 8–10° to avoid sudden freezing and crystallization which might otherwise result in an explosion. The mixture was carefully introduced into a separatory funnel and the alkaline layer tapped out. The aqueous dioxan solution of diazomethane thus obtained was used immediately.

In most cases, there was some evolution of N_2 during the first few hr and it was necessary to cool the reaction mixture to 15–20° until gas evolution subsided. The N_2 resulted from simple decomposition of diazomethane, as no ethylenimine formation was noticed.

An additional amount of dioxan (25–75ml) was used to effect complete solution in the case of sparingly soluble anils.

The 1,2,3-triazolines were obtained invariably as pure crystalline products which needed no further purification except for purposes of microanalyses. In certain cases, where the anils were ether soluble, small amounts of unreacted materials were removed by stirring the air dried product with diethyl ether at R.T.

The triazolines resulting from liquid anils were obtained by treating the cooled reaction mixture with a large excess of cold water when a semisolid material separated out. This was stirred well with a small amount of pet. ether (25–30 ml) when the unreacted oily anil went into solution and the triazoline adduct solidified into a crystalline mass. This was filtered and washed twice with small amounts of pet. ether giving a very pure product which needed no further crystallization.

The halogen bearing triazolines (1- and 5-*p*-chlorophenyl, 1-*p*-bromophenyl and 1,5-bis-*p*-chlorophenyl) presented difficulties. They always precipitated along with small amounts of unreacted anil, and showed a wide range in their m.ps. The unreacted anils could be removed only by boiling the product with 95% EtOH, cooling to R.T. and filtering out the insoluble triazoline. This process was repeated two to three times, as necessary, until sharper m.p.s were obtained. A final crystallization from acetone yielded the pure product.

The 1-*p*-anisyl-5-*m*-nitrophenyl-1,2,3-triazoline was an exceptional case. The reaction mixture yielded a red oil which failed to solidify. It was extracted with ether, dried over $MgSO_4$ and treated with excess pet. ether. A red oil separated out and was rejected. The yellow supernatant on standing slowly deposited some crystals. This was filtered and crystallized from acetone.

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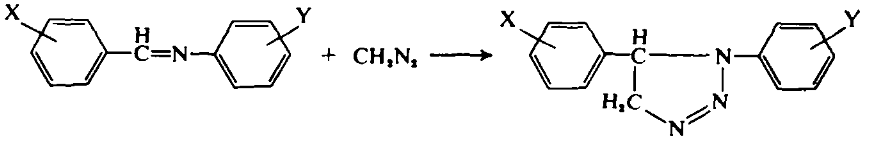
[11] F. Arndt, *Organic Syntheses*, Coll. Vol. II. 165 (1943).

TABLE 2. SYNTHESES OF 1,2,3-TRIAZOLINES



Substituent		Schiff bases		1,2,3-Triazolines					
C-Phenyl (X)	N-Phenyl (Y)	M.p. or B.P.	Yield %	Reaction time (hr)	Crystallization solvent[a]	Yield (%)[b]	M.p.	Nitrogen % Calc.	Nitrogen % Found
H	H	52°	75	192	E	53·3	130–131°[c]	—	—
m-NO_2	H[d]	65–66·5°	66	96	A	43.8	146–147°	20·89	21·10
p-NO_2	H[d,e]	92–93°	70	96	B	45·0	130–130·5°	—	—
H	*m*-NO_2[d]	71–74°	79	118	A	(68·0)	107–108°	20·89	21·02
				43[f]		(67·5)			
H	*p*-NO_2[d,e]	118–119°	50	42	A	(75·0)	152–153°	—	—
o-NO_2	*m*-NO_2	129–130°	60	15	A	(92·5)	145–146°	22·36	22·50
m-NO_2	*m*-NO_2	158·5–160°	80	52	A	70·0	144–145°	22·36	22·42
p-NO_2	*m*-NO_2	153–154°	85	96	A-P	(90·0)	143–144°[g]	22·36	22·53
p-NO_2	*p*-NO_2	200–202°	81	45	ET or A	72·5	172·5–173·5°[h]	22·36	22·44
o-Cl	H	162–164·5°	30[i]	98	A-P	(56·4)	98·5–101°	16·31	16·24
		(4·5 mm)							
p-Cl	H	63–64°	70	168	E	41·0	127–129°[j]	—	—
H	*m*-Cl	165–165·5°	76	97	A-P	(59·0)	73–74·5°	16·31	16·53
		(3·0 mm)							
H	*p*-Cl[e]	62–62·5°	93	96	E	64·1	128–132°	—	—
H	*p*-Br	65–67·5°	77	53	A	44·4	143–146°	13·91	14·03
							C%	55·63	55·78
							H%	3·97	4·07

o-Cl	*p*-Br	66–67·5°	95	54	A	(90)	156–157·5°	12·45	12·49
p-Cl	*p*-Cl	109–110·5°	90	96	A	45·4	131–133·5°	14·38	14·40
o-Cl	*m*-NO_2	114–116°	95	28	A	(92·0)	118·5–120°	18·51	18·59
p-Cl	*m*-NO_2	124–125·5°	78·5	96	A–P	60·0	121·5–124·5°	18·51	18·60
m-NO_2	*m*-Cl	101–104°	86	96	A–P	44·4	105–106°	18·51	18·66
m-NO_2	*p*-Cl	85–86°	89	51	A	(87·0)	164–165°	18·51	18·62
m-NO_2	*p*-Br	83–84°	75	66	A	(71·2)	167–167·5°	16·15	16·38
p-NO_2	*m*-Cl	108–110°	92	97	A–P	75·6	139–140°	18·51	18·58
p-NO_2	*p*-Br[d]	162–164°	92	72	—[k]	70·0	164–165°	—	—
o-CH_3	H	150–152° (4·5 mm)	79	112	A–P	(28·0)	96·5–98·5°	17·72	17·82
H	*m*-CH_3	155·5–156° (3·0 mm)	90	168	E	(40·0)	81–83·5°	17·72	17·80
H	*p*-CH_3	154° (2·0 mm)	87	168	E	(26·0)	114–116°	17·72	17·76
m-NO_2	*p*-OCH_3	65–67·5°	81	144	A	22·2	113–114·5°	18·79	18·82

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[a] E, ethanol; A, acetone; B, benzene; A–P, acetone–pet. ether mixture; ET, ethyl acetate.

[b] The figures given in parentheses refer to yields of triazoline adducts isolated directly from the reaction mixture as indicated in the Experimental Section, in pure form. They had m.ps same as the analytical samples obtained by crystallization from the indicated solvents.

[c] Lit. 5, m.p. 128°; see also Table 3.

[d] 0·03 mole of anil was reacted with 0·06 mole of diazomethane in 100 ml dioxan.

[e] Lit. 1.

[f] Reacted 0·015 mole of anil with 0·05 mole of diazomethane.

[g] Lit. 4, reported no yield and an erroneous m.p. 128–129°.

[h] 0·02 mole of anil was reacted with 0·04 mole of diazomethane in 170 ml of dioxan. Lit. 4 reported no yield and a m.p. 180–181°; Lit. 5, m.p. 178°

[i] The low yield is due to extensive decomposition during distillation.

[j] Lit. 5, m.p. 128°; see also Table 3.

[k] The crystals separated out directly from the reaction mixture. The filtrate, on dilution with water, yielded more product which was crystallized from benzene. Lit. 4, no yield given and m.p. 161°.

No attempt was made to identify the red oil. It had a characteristic unpleasant odour reminiscent of isonitriles. The formation of minor quantities of a red sticky material with the same odour was also noticed in the case of 1-phenyl-5-*m*-nitrophenyl-1,2,3-triazoline.

The 1,5-diaryl-1,2,3-triazolines had characteristic well defined crystal shapes and were large, shiny and gritty in nature. Those bearing one or more nitro groups were yellow in colour; all others were colourless. They underwent slow decomposition on standing for about 1–2 months and gave rise to deep yellow or orange products (from the colourless and yellow triazolines respectively), with the same unpleasant odour mentioned earlier. The majority of the triazolines melted with violent decomposition and evolution of N_2 yielding bright red or orange coloured melts.

The syntheses of the various 1,2,3-triazolines are listed in Table 2, along with other pertinent data.

RESULTS AND DISCUSSION

The results do not reveal any general dependence of rate on the dielectric constant of the solvent (Table 1) and it appears from these solvent effects that the cycloaddition of diazomethane to Schiff bases follows essentially a one-step concerted process. A discrete zwitterion intermediate (I) does not seem to exist; but an active complex with partial dipolar character appears to be formed, in the transition state, which would explain the electronic substituent effects reported earlier (1). The transition complex may be considered as approximating to the structure (II), the carbon–carbon bond formation (II, a) having progressed to a greater extent than the nitrogen–nitrogen bond formation (II, b), with the consequent development of partial charge as indicated. Electron withdrawing substituents on the N-phenyl would then enhance the rate, as a result of stabilization of negative charge on the nitrogen attached to this ring, in the transition complex.

The results in Table 1 also indicate a sizeable increase in rate in the presence of small amounts of water—a solvent which has a high degree of association and which is known to be a good solvating solvent for ions. Since the rate is not primarily dependent on the dielectric constant of the solvent, the mechanism by which water catalyzes the reaction is not clear; it could be an effect of hydrogen bonding involving water-substrate interaction in the transition state or could probably be a simple medium effect, resulting in an ordering in the solvent matrix. A similar acceleration in rate in the presence of ethyl alcohol and glycol monomethyl ether is apparent in the results reported by Huisgen for the cycloaddition of diphenyldiazomethane on to dimethylfumarate.[8] Water and other associated solvents such as the alcohols are also known to catalyse the addition reactions of diazoalkanes to carbonyl compounds.[12] Further studies in this direction, involving catalysis of the cycloaddition of diphenyldiazomethane to Schiff bases by different protic solvents,[13] are being carried out, with a view to obtain a satisfactory explanation for the role of water and other solvents in the catalysis.

The significant effect of water on the reaction rate makes possible the cycloaddition of diazomethane to Schiff bases, a convenient general method of great utility for the synthesis of many 1,5-aryl-substituted-1,2,3-triazolines, comparable in value to pyrazoline synthesis by the addition of diazoalkanes to olefins. In earlier attempts[4,5] to react diazomethane with Schiff bases, dry etheral solutions of diazomethane were used and the results have been largely unsuccessful, even the very reactive anils yielding only very small amounts of the adduct. By carrying out the cycloaddition in aqueous dioxan solutions, it has now been found that a large variety of Schiff bases react with

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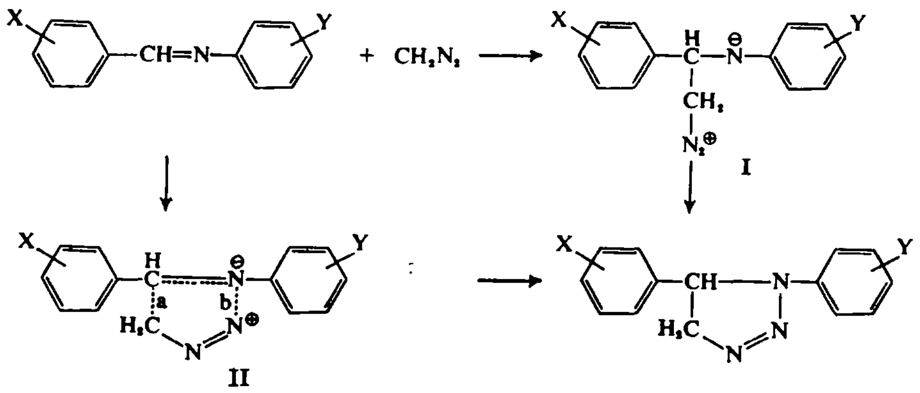
[12] C. D. Gutsche, *Organic Reactions*, Vol. VIII; p. 395. Wiley, New York, N.Y. (1954).

[13] P. K. Kadaba, unpublished results.



diazomethane and the 1,2,3-triazoline addition products are obtained in good yields. Dioxan has been chosen as the solvent for the reaction, in view of its easy miscibility with water and the ease with which it can be substituted for diethyl ether in the preparation of diazomethane.[11] In the case of anils bearing active groups (nitro or nitro and chloro) yields as high as 70–90% of the pure adduct have been obtained. Even those anils containing no active groups give very satisfactory results, far superior to those obtained by the addition of aryl azides to olefins.[5,6]

A comparison of the yields obtained in selected cases using dry and undried solutions of diazomethane in benzene, diethyl ether and dioxan respectively is given in Table 3. While the reaction fails altogether in anhydrous ether and even in wet ethereal solutions the yields are too low to be of preparative value, consistently better yields are obtained in aqueous dioxan solutions. As the solvents themselves have little effect on the rate (Table 1) the low yield in benzene and ether is attributed to the limited

TABLE 3. COMPARISON OF 1,2,3-TRIAZOLINE FORMATION IN VARIOUS SOLVENTS

Substituent		Yield % of 1,2,3-triazoline in				
		Anhydrous		Wet		
C-Phenyl (X)	N-Phenyl (Y)	Ether	Ether + Methanol	Benzene	Ether	Dioxane
H	H	Nil(48)[a]	10(240)[b]	—	10(240)[c]	53·3(192)[d]
H	*m*-NO_2	35(64)[d]	—	51(47)[d]	—	67·5(43)[d]
p-NO_2	H	—	—	—	25(96)[c]	45(96)[c]
p-NO_2	*p*-NO_2	Positive reaction (48)[a]	91(240)[b]	—	—	72·5(45)[d]
o-NO_2	H	5(18)[c]	25(21)[c]	—	25(21)[c]	76·0(48)[d]
H	*p*-Cl	—	—	21·8(98)[d]	22(96)[c]	64·1(96)[d]
p-Cl	H	—	10(240)[b]	—	—	41(168)[d]
H	*p*-Br	Nil(48)[a]	—	—	—	44·4(53)[d]

[a] Text Ref. 4; figures in parentheses refer to reaction time in hr. In the case of *p*-nitrobenzal *p*-nitroaniline reaction occurred, but no yield is recorded.

[b] Text Ref. 5.

[c] Text Ref. 1.

[d] Present work.

miscibility of these solvents with water. In the course of the present work, about thirty variously substituted 1,5-diaryl-1,2,3-triazolines have been synthesized employing the cycloaddition reaction in aqueous dioxan, and the general applicability of this method of synthesis established.

In view of the increasing interest in the 1,2,3-triazoline compounds as a potential source for the synthesis of aziridines by photodecomposition reactions,[14] development of facile methods of syntheses is important. At present only two methods are available for 1,2,3-triazoline synthesis. Of these, the cycloaddition of aryl azides to olefinic double bonds, is of little value to the synthesis of 1,5-diaryl triazolines, since, only strained double bonds in cyclic compounds are susceptible to this addition and reaction is very sluggish when the double bond is in conjugation with an aromatic system.[5,15] The addition of cyanogen azide, a highly reactive organic azide, to olefins, reported recently,[16] proceeds rapidly; the triazolines formed in this reaction, however, are generally very unstable and decompose *in situ* giving rise to alkylidene cyanamides and/or N-cyanoaziridines. The second method dealing with the rearrangement of 1-aryl azoaziridines yields the 1-aryl triazolines but needs the aziridines themselves as starting materials.[17] Thus, at the present time, the cycloaddition of diazomethane to Schiff bases in aqueous dioxan solutions appears to be the only general method for the synthesis of the 1,5-diaryl-1,2,3-triazolines.

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[14] P. Scheiner. *J. Org. Chem.* **30**, 7 (1965).

[15] J. H. Boyer and F. C. Canter, *Chem. Revs.* **54**, 1 (1954).

[16] F. D. Marsh and M. E Hermes, *J. Amer. Chem. Soc.* **86**, 4506 (1964).

[17] H. W. Heine and D. A. Tomalia, *J. Amer. Chem. Soc.* **84**, 993 (1962).