Microwave-Assisted 1,3-Dipolar Cycloaddition. Synthesis of Substituted 9-(1,2,3-Triazol-1-yl)acridines

E. VEVERKOVÁ and Š. TOMA

Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, SK-842 15 Bratislava
e-mail: veverkova@fns.uniba.sk

Received 20 October 2004

Syntheses of substituted 9-(1,2,3-triazolyl)acridines *via* 1,3-cycloaddition reactions of 9-azidoacridine with various acetylenes were realized in short time with appreciable yields under microwave irradiation.

The organic azides react with olefins and acetylenes to yield triazolines and triazoles rather sluggishly [1, 2]. In spite of this fact these reactions make the powerful class of "click reaction" [3]. Several papers were published recently describing [2 + 3] cycloaddition reactions of aliphatic and aromatic azides with substituted acetylenes [4], acylcyanides [5], and sulfonylcyanides [6]. Published procedures have a broad application but in all cases a very long reaction time (16—100 h) was required.

The beneficial effect of microwave irradiation on several cycloadditions [7, 8] and particularly for 1,3-dipolar cycloadditions [9] is documented. However, probably due to concerns of safety of the azide moiety only one study was published describing cycloaddition of azidomethyldiethylphosphonate with acetylenes under microwave irradiation [10].

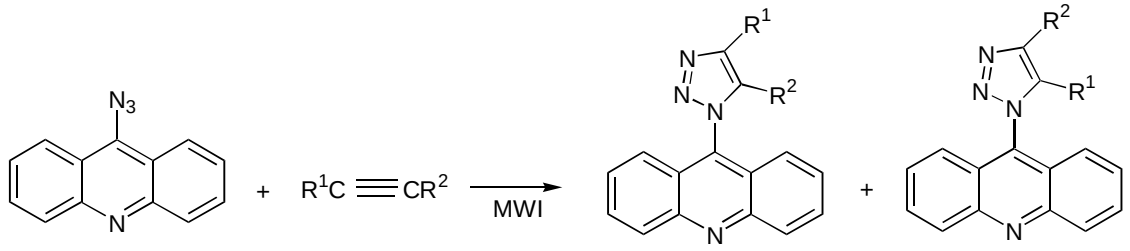
We describe herein the attempts to increase the reaction rate of 1,3-dipolar cycloaddition reactions of 9-azidoacridines with various acetylenes using microwave irradiation (Scheme 1). To start the investigation we tried to determine the optimal reaction conditions. The solvent-free reaction of 9-azidoacridine *I* with dimethylacetylene dicarboxylate *IIa* was performed. After 3 min irradiation the temperature of the reaction mixture reached 200 °C and complicated mixture of decomposition products was obtained containing just very low amount of product *IIIa*. Next we lowered the final temperature under 100 °C (reaction time 1 min) but the mixture of different products with high ratio of starting azide was obtained again. We decided therefore to perform the reaction in the solvent and toluene was chosen as the reaction medium. Reaction was complete after 30 min of microwave irradiation at temperature 80 °C (power 25—35 W) (Table 1, Entry 1). At higher temperature the decomposition of the starting azide was noted again.

The reactions of 9-azidoacridine with various unsymmetrically substituted acetylenes were performed at similar conditions (Table 1, Entries 2—8), but reaction time had to be prolonged to 60 min. The reaction of 9-azidoacridine with triethylsilylacetylene (Entry 8) afforded cycloadduct *IIIh* as the only isolable product, which is in conformity with the results of classical experiments reported in [4]. In other cases mixtures of two triazole regioisomers were obtained. As it follows from Table 1, 9-(4-R-triazolyl)acridines *IIIb*—*IIIg* were the major products in all cases.

The structures of the triazole regioisomers were confirmed by ^{1}H NMR spectra. NOE difference experiments had to be used to assign the structures of isomers *IIIb* and *IVb* because our ^{1}H NMR spectral data were not identical with published data of corresponding regioisomers reported in [4]. Irradiation of the triazole 5′-proton of compound *IIIb* caused a 4.6 % NOE enhancement of the acridine doublet at $\delta = 7.43$ assigned to the identical 1-(or 8-)proton. Irradiation of this acridine proton gave 21.5 % enhancement of the triazole 5′-proton signal. Small enhancement was detected in the irradiation of 4′- (0.4 %), resp. 1-(or 8-)-protons (4 %) in the related irradiation experiments with compound *IVb*. The structures of *IIIe* and *IVe*, the spectra of which were not identical with published data in [4], were assigned on the basis of comparison of the ^{1}H NMR data with compounds *IIIf*, *IVf* in combination with *IIIb*, *IVb*.

The signals of methyl, ethyl, and methoxycarbonyl groups in spectra of the major product *IIIb, IIIc, IIIf* appeared at $\delta = 0.4$—0.8 downfield of the corresponding signals of the minor isomers *IVb, IVc, IVf*. Similarly, the signal of methylene group in 4-substituted triazoles *IIIc, IIIg* displayed a significant downfield shift (0.39, 0.62) in comparison with corresponding signal in 5-substituted isomers (*IVc, IVg*). These differences of enhancements are probably due to the ring current effect of 9-acridine skeleton.

It is known that the specific (not purely thermal) microwave effect can be observed in cycload-



I *II* *III* *IV*

	R^1	R^2
a	$COOCH_3$	$COOCH_3$
b	$COOCH_3$	H
c	$CH_2OCOC_2H_5$	H
d	$COOC_2H_5$	CH_3
e	Ph	H
f	$COOCH_3$	Ph
g	CH_2Br	H
h	$Si(CH_3)_3$	H

Scheme 1

Table 1. Microwave-Assisted Preparation of Substituted 9-(1,2,3-Triazol-1-yl)acridines

Entry	Alkyne	Time/min	Yield *III* + *IV*/%	Yield *III* + *IV*/%[a]	*w*(*III*)/*w*(*IV*)[b]
1	*IIa*	30	92	46	
2	*IIb*	60	78	67	78 : 22
4	*IIc*	60	72		60 : 40
5	*IId*	60	55		77 : 23
6	*IIe*	60	67	49	64 : 36
8	*IIf*	60	81		70 : 30
9	*IIg*	60	82		68 : 22
10	*IIh*	60	92	49	100 : 0

a)Yields of classical experiments (thermal heating, 24—48 h) reported in [4].
b) Determined by ^{1}H NMR analysis.

dition reactions when dienes and/or dienophiles are unsymmetrical, which was explained by developing of charges in the transition state [11]. We decided to check if some specific microwave acceleration will be observed also in our cases. Some experiments with thermal heating at the final temperature (80 °C) were performed (Table 2). From the results it is possible to see that considerable microwave effect was observed because yields were nearly doubled in microwave experiments in comparison with experiments under thermal heating. The effect is higher in the case of less activated acetylene (Table 2, Entry 2), which is in accord with the reported data [10].

In conclusion, the rate of 1,3-dipolar cycloaddition reactions of 9-azidoacridines with various acetylenes can be accelerated by running the reactions under microwave irradiation at temperature under 100 °C. Decomposition of 9-azidoacridine was observed when the higher temperature or solvent-free conditions were used.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were measured on Varian Gemini 2000 instrument at 300 MHz and 75 MHz. DMSO was used as the solvent and tetramethylsilane as an internal standard. Microanalyses were carried out on an Erba (Strumenstacione, Milano) CHN analyzer, model 1106. These results agreed with the calculated values. Melting points were determined on a Kofler apparatus. All microwave experiments were carried out in a SYNTHEWAVE 402® PROLABO reactor. The temperature of reaction mixture was monitored by an IR thermometer.

General Procedure

A mixture of 9-azidoacridine (0.005 mol) and appropriate acetylene (0.015 mol) in toluene (10 cm^3) was microwave-irradiated in the microwave reactor at 80 °C (25—35 W input power) for the time as indicated in Table 1. After cooling the solvent was re-

Table 2. Thermal or Microwave Activation for the Cycloaddition of 9-Azidoacridine with Some Acetylenes

Entry	R^1	R^2	Activation	Conditions		Total yield/%
				t/min	θ/°C	
1	$COOCH_3$	H	Δ	60	80	42
			MWI	60	80	78
2	Ph	H	Δ	60	80	28
			MWI	60	80	65

moved by vacuum evaporation. The crude products were purified by column chromatography on silica using isohexane—ethyl acetate (φ_r = 2 : 1) as the eluent. The high purity of each of two isomers was reached by crystallization from ethanol or the mixture isohexane—ethyl acetate. Yields, melting points, and spectral data of triazolylacridines are as follows:

Dimethyl 1-(acridin-9-yl)-1,2,3-triazole-4,5-dicarboxylate (*IIIa*): Yield 92 %, m.p. = 153—154 °C (138 °C [4]). NMR spectra were found to be identical with the data described in literature [4].

Methyl 1-(acridin-9-yl)-1,2,3-triazole-4-carboxylate (*IIIb*): Yield 61 %, m.p. = 262—263 °C (208—210 °C [4]). ^{1}H NMR, δ: 3.95 (s, 3H, CH_3), 7.43 (d, 2H, J = 8.7 Hz, H_{arom}), 7.73 (dt, 2H, J = 1.5 Hz, J = 6.6 Hz, H_{arom}), 8.00 (dt, 2H, J = 1.5 Hz, J = 6.6 Hz, H_{arom}), 8.36 (d, 2H, J = 8.7 Hz, H_{arom}), 9.61 (s, 1H, H-5′). ^{13}C NMR, δ: 52.1, 121.6, 122.3, 128.9, 129.4, 131.4, 133.3, 136.6, 139.5, 148.6, 160.5.

Methyl 1-(acridin-9-yl)-1,2,3-triazole-5-carboxylate (*IVb*): Yield 17 %, m.p. = 194—195 °C (241 °C [4]). ^{1}H NMR, δ: 3.61 (s, 3H, CH_3), 7.25 (d, 2H, J = 8.7 Hz, H_{arom}), 7.69 (dt, 2H, J = 1.5 Hz, J = 6.6 Hz, H_{arom}), 7.98 (dt, 2H, J = 1.5 Hz, J = 6.6 Hz, H_{arom}), 8.35 (d, 2H, J = 8.7 Hz, H_{arom}), 8.89 (s, 1H, H-4′). ^{13}C NMR, δ: 52.8, 122.0, 122.1, 128.8, 129.4, 131.3, 131.8, 137.1, 137.8, 148.6, 157.2.

9-(4-Propionyloxymethyl-1,2,3-triazol-1-yl)acridine (*IIIc*): Yield 48 %, m.p. = 141—143 °C. ^{1}H NMR, δ: 1.09 (t, 3H, CH_3), 2.44 (q, 2H, CH_2), 5.40 (s, 2H, CH_2), 7.37 (d, 2H, J = 8.7 Hz, H_{arom}), 7.74 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.00 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.94 (s, 1H, H-5′), 8.35 (d, 2H, J = 8.7 Hz, H_{arom}). ^{13}C NMR, δ: 8.9, 26.6, 56.8, 121.5, 122.1, 128.5, 128.7, 129.3, 131.2, 137.2, 142.8, 148.6, 173.4.

9-(5-Propionyloxymethyl-1,2,3-triazol-1-yl)acridine (*IVc*): Yield 24 %, m.p. = 113—115 °C. ^{1}H NMR, δ: 0.46 (t, 3H, CH_3), 1.59 (q, 2H, CH_2), 5.00 (s, 2H, CH_2), 7.48 (d, 2H, J = 8.1 Hz, H_{arom}), 7.73 (dt, 2H, J = 1.3 Hz, J = 6.9 Hz, H_{arom}), 8.00 (dt, 2H, J = 1.3 Hz, J = 6.9 Hz, H_{arom}), 8.34 (s, 1H, H-4′), 8.36 (d, 2H, J = 8.1 Hz, 2H_{arom}). ^{13}C NMR, δ: 8.2, 25.8, 53.1, 121.6, 122.2, 122.3, 128.8, 129.5, 131.4, 134.6, 136.5, 142.9, 148.7, 172.2.

Ethyl 1-(acridin-9-yl)-5-methyl-1,2,3-triazole-4-carboxylate (*IIId*): Yield 34 %, m.p. = 199—201 °C. ^{1}H NMR, δ: 1.40 (t, 3H, CH_3), 2.27 (s, 3H, CH_3), 4.43 (q, 2H, CH_2), 7.37 (d, 2H, J = 8.7 Hz, H_{arom}), 7.74 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.02 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.39 (d, 2H, J = 8.7 Hz, H_{arom}). ^{13}C NMR, δ: 9.1, 14.2, 60.7, 121.9, 122.1, 129.1, 129.5, 131.5, 135.0, 136.2, 142.2, 148.7, 160.9.

Ethyl 1-(acridin-9-yl)-4-methyl-1,2,3-triazole-5-carboxylate (*IVd*): Yield 21 %, m.p. = 137—139 °C. ^{1}H NMR, δ: 0.67 (t, 3H, CH_3), 2.72 (s, 2H, CH_3), 3.89 (q, 2H, CH_2), 7.32 (d, 2H, J = 8.1 Hz, H_{arom}), 7.71 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 7.95 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.34 (d, 2H, J = 8.1 Hz, H_{arom}). ^{13}C NMR, δ: 11.9, 13.0, 61.4, 122.1, 128.4, 128.6, 129.3, 131.2, 137.9, 147.9, 148.6, 157.2.

9-(4-Phenyl-1,2,3-triazol-1-yl)acridine (*IIIe*): Yield 57 %, m.p. = 281—282 °C (239 °C [4]). ^{1}H NMR, δ: 7.53—7.58 (m, 5H, H_{arom}), 7.74 (dt, 2H, J = 1.5 Hz, J = 6.6 Hz, H_{arom}), 8.04 (m, 4H, H_{arom}), 8.35 (d, 2H, J = 8.7 Hz, H_{arom}), 9.40 (s, 1H, H-5′). ^{13}C NMR, δ: 121.4, 122.4, 125.5, 125.7, 128.4, 128.6, 129.0, 129.3, 129.4, 131.2, 137.2, 147.0, 148.6.

9-(5-Phenyl-1,2,3-triazol-1-yl)acridine (*IVe*): Yield 23 %, m.p. = 239—241 °C (249—250 °C [4]). ^{1}H NMR, δ: 7.08—7.20 (m, 5H, H_{arom}), 7.39 (d, 2H, J = 8.7 Hz, H_{arom}), 7.69 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 7.98 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.37 (d, 2H, J = 8.7 Hz, H_{arom}), 8.57 (s, 1H, H-4′). ^{13}C NMR, δ: 122.1, 122.2, 127.1, 128.9, 129.0, 129.6, 131.4, 132.9, 136.9, 140.7, 148.7.

Methyl 1-(acridin-9-yl)-5-phenyl-1,2,3-triazole-4-carboxylate (*IIIf*): Yield 61 %, m.p. = 223—225 °C. ^{1}H NMR, δ: 3.84 (s, 3H, CH_3), 6.94—7.25 (m, 5H, H_{arom}), 7.59 (d, 2H, J = 8.7 Hz, H_{arom}), 7.70 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 7.95 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.26 (d, 2H, J = 8.7 Hz, H_{arom}). ^{13}C NMR, δ: 52.0, 122.1, 122.4, 124.7, 128.0, 129.1, 129.2, 129.4, 130.1, 131.4, 135.5, 136.3, 144.2, 148.5, 160.7.

Methyl 1-(acridin-9-yl)-4-phenyl-1,2,3-triazole-5-carboxylate (*IVf*): Yield 20 %, m.p. = 184 °C. ^{1}H NMR, δ: 3.41 (s, 3H, CH_3), 7.47 (d, 2H, J = 8.7 Hz, H_{arom}), 7.50—7.61 (m, 3H, H_{arom}), 7.72 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 7.93—8.03 (m, 4H, H_{arom}), 8.37 (d, 2H, J = 8.7 Hz, H_{arom}). ^{13}C NMR, δ: 53.5, 122.9, 123.1, 128.9, 129.2, 129.7, 130.1, 130.3, 130.4, 132.2, 138.5, 149.5, 149.9, 158.8.

9-(4-Bromomethyl-1,2,3-triazol-1-yl)acridine (*IIIg*): Yield 55 %, m.p. = 173—175 °C. ^{1}H NMR, δ: 5.00 (s, 2H, CH_2), 7.37 (d, 2H, J = 8.7 Hz, H_{arom}), 7.75 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.01 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.35 (d, 2H, J = 8.7 Hz, H_{arom}), 8.99 (s, 1H, H-5′). ^{13}C NMR, δ: 22.8, 121.6, 122.1, 122.4, 128.5, 128.7, 129.4, 131.3, 132.0, 137.2, 144.6, 148.7.

9-(5-Bromomethyl-1,2,3-triazol-1-yl)acridine (*IVg*): Yield 27 %, m.p. = 142—143 °C. ^{1}H NMR, δ: 4.55 (s, 2H, CH_2), 7.27 (d, 2H, J = 8.7 Hz, H_{arom}), 7.73 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.02 (dt, 2H, J = 1.5 Hz, J = 7.5 Hz, H_{arom}), 8.36 (d, 2H, J = 8.7 Hz, H_{arom}), 8.39 (s, 1H, H-4′). ^{13}C NMR, δ: 22.1, 116.4, 119.5, 120.0, 121.3, 125.0, 127.9, 128.4, 130.5, 135.5, 139.9.

9-(4-Trimethylsilyl-1,2,3-triazol-1-yl)acridine (*IIIh*): Yield 92 %, m.p. = 206—208 °C (208 °C [4]). NMR spectra were found to be identical with the data described in literature [4].

Acknowledgements. Our thanks are due to Dr. B. Horváth from the Institute of Chemistry, Faculty of Natural Sciences, Comenius University for NOE experiments. This work was carried out under the auspices of COST D32 project and financial help of the Ministry of Education of the Slovak Republic (VTP project No. 1012/2003) is acknowledged.

REFERENCES

1. Boyer, J. H. and Canter, F. C., *Chem. Rev. 54*, 1 (1954).
2. Hlasta, D. J. and Ackerman, J. H., *J. Org. Chem. 59*, 6184 (1994).
3. Kolb, H. C., Finn, M. G., and Sharpless, K. B., *Angew. Chem., Int. Ed. Engl. 40*, 2004 (2001).
4. Hagan, D. J., Chan, D., Schwalbe, C. H., and Stevens, M. F. G., *J. Chem. Soc., Perkin Trans. 1*, 915 (1998).
5. Zachary, P. D. and Sharpless, K. B., *Angew. Chem., Int. Ed. Engl. 41*, 2113 (2002).
6. Zachary, P. D. and Sharpless, K. B., *Angew. Chem., Int. Ed. Engl. 41*, 2110 (2002).
7. Carrillo, J. R., de la Cruz, P., Diaz-Ortiz, A., Gomez-Escalinilla, M. J., de la Hoz, A., Langa, F., Moreno, A., and Prieto, P., *Recent Res. Dev. Org. Bioorg. Chem. 1*, 68 (1997).
8. Carrillo, J. R., Diaz-Ortiz, A., Cossio, F. P., Gomez-Escalinilla, M. J., de la Hoz, A., Moreno, A., and Prieto, P., *Tetrahedron 56*, 1569 (2000).
9. Rigolet, S., Goncalo, P., Melot, J. M., and Vebrel, J., *J. Chem. Res., Miniprint 48*, 2813 (1998).
10. Louerat, F., Bougrin, K., Loupy, A., Ochoa de Retana, A. M., Pagalday, J., and Palacios, F., *Heterocycles 48*, 161 (1998).
11. Perreux, L. and Loupy, A., *Tetrahedron 57*, 9199 (2001).