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Dedicated to Professor Ionel Haiduc
on the occasion of his 65th birthday

APPLICATION OF PHASE TRANSFER CATALYSIS IN ACRIDINE SERIES VIII[1]. SYNTHESIS OF 9-(1,2,3-TRIAZOL-1-YL)ACRIDINES

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ABSTRACT. The syntheses of 9-(1,2,3-triazol-1-yl)acridine derivatives have been achieved by phase transfer catalyzed cyclisation reaction of 9-azidoacridine with either 1,3-dicarbonyl compounds or activated acetonitriles.

INTRODUCTION

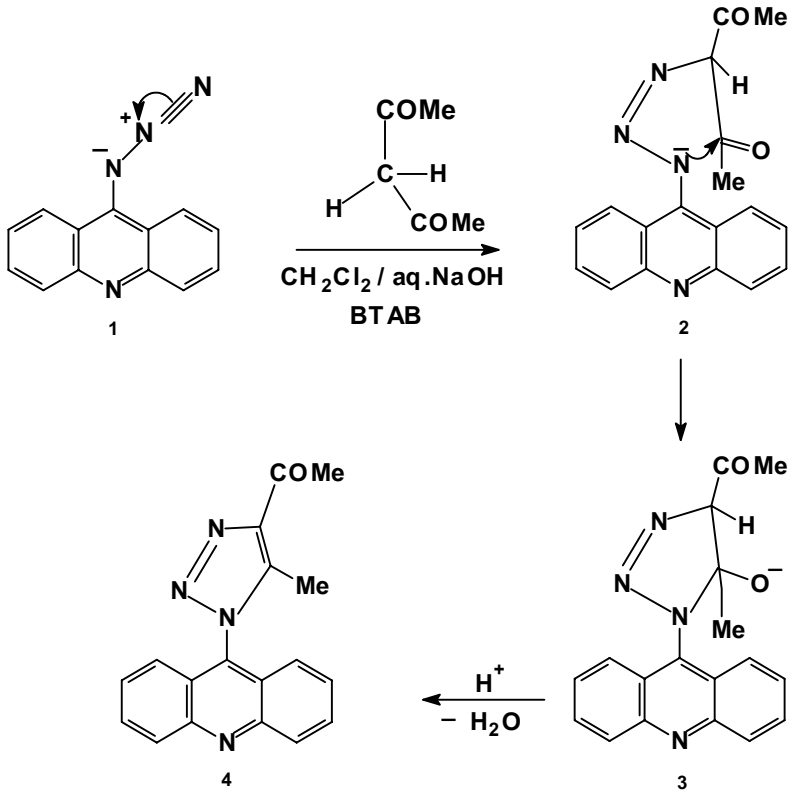
Acridine derivatives have attracted the attention of medicinal chemists because of their broad-ranging biological properties[2]. In recent years the DNA binding propensities and topoisomerase II-inhibitory activities of acridines have been exploited in the development of clinically-active antitumor agents[3]. A derivative of a related pyridoacridine, 7-aminopyrido[2,3-c]acridine, has been shown to inhibit human gastric carcinoma MKN 45 cells: the planar aromatic tetracycle is more active than the 5,6-dihydroanalogue[4]. A series of polycyclic aromatic compounds based on 3H-pyrido[2,3,4-kl]acridine have been isolated from natural (marine) sources[5] and also shown to inhibit topoisomerase II.

Julino and Stevens[6] have exploited the Graebe Ullmann degradation[7] to construct 7H-pyrido[4,3,2-kl] acridine ring system using appropriate 9-(1,2,3-triazolyl)acridines as starting materials.

In the course of our project directed towards the development of new anticancer derivatives[8] we now report the synthesis of 9-(1,2,3-triazol-1-yl)acridines from 9-azidoacridine and reactive methylenic compounds using phase transfer catalysis. This route, comparatively with classic procedure[6], has the advantage of using nonanhydrous solvents, a more simple work-out of the reaction products and better yields.

RESULTS AND DISCUSSSION

It is well known that organic azides undergo base-catalyzed condensation reactions with activated methylenic compounds[9]. In order to prepare 9-triazolylacridine derivatives we used commercially available 1,3-dicarbonyl compounds as reaction partners of 9-azido-acridine[10]. When a dichloromethane solution of the azidoacridine **1**, was allowed to react with an excess of pentane-2,4-dione, in presence of tetrabutylammonium bromide (TBAB) as catalyst and of aqueous sodium hydroxide solution at room temperature, the corresponding 9-(1,2,3-triazol-1-yl)acridine **4** were obtained with 80% yield, comparatively with 65% by classical procedure (see Scheme 1).[6]



1 2 3 4

Scheme 1.

In contrast with previous procedure[6] the reaction didn't occur with keto-esters, likely due to the hydrolysis of the ester group.

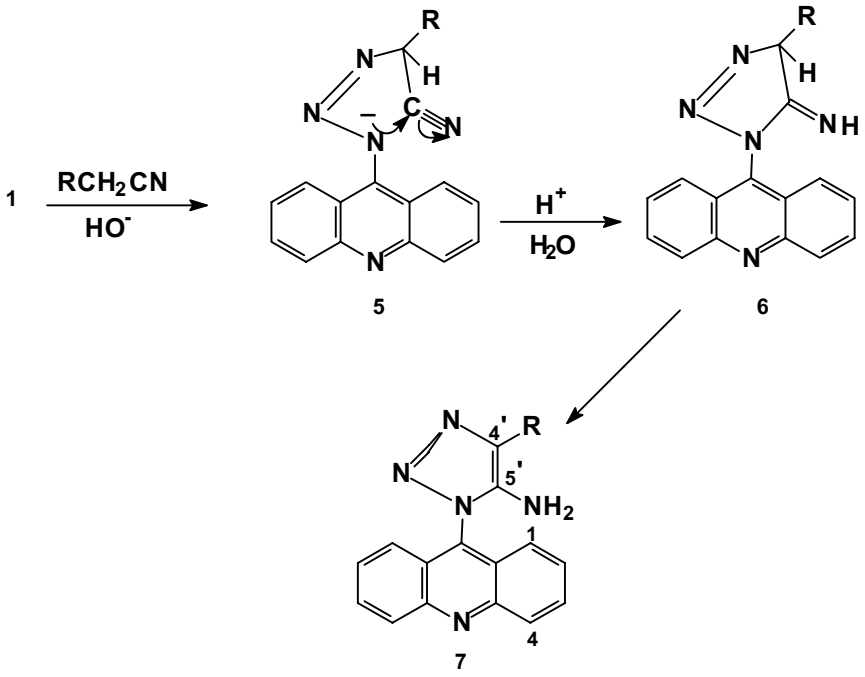
In order to obtain the amino-substituted triazolylacridines from 9-azidoacridine **1**, activated acetonitriles were employed as the reactive methylenic parts, using the same technique as above (see Scheme 2).

The results of our experiments are shown in Table 1. The reaction is most likely directed by a bonding overlap of the LUMO of 9-azidoacridine and the HOMO of the α-methylene carbon of the carbanions.

Table 1

Compounds **7** prepared by PTC.

Nr. crt.	R	m.p. (lit.m.p.) (^{0}C)	η (lit. η) (%)
1.	- CN	249 –251 (248-250)	60 (47)
2.	- Ph	206-208 (207-209)	90 (76)
3.	-C_6H_4Cl-o	165-167 (167-169)	85 (73)
4.	-$CONC_5H_{10}$	231--233 (230-232)	50(26)



Scheme 2.

CONCLUSIONS

We obtained 9-(1,2,3-triazol-1-yl)- and 9-(amino-1,2,3-triazol-1-yl)-acridines by a more convenient procedure using phase transfer catalysis comparatively with the classical way[6]. Because of hydrolysis reaction of the ester group, the β-keto-esters could not be used as reaction partners in PTC method.

EXPERIMENTAL.

Melting points are uncorrected. The NMR spectra were recorded on Varian Gemini 300 spectrometer, in $CDCl_3$ or in DMSO.

9-(4-Acetyl-5-methyl-1,2,3-triazol-1-yl)acridine. 9-Azidoacridine (165 mg, 0.75 mmol), pentane-2,4-dione (150 mg, 0.75 mmol), and tetrabutylammonium bromide (1.00 molar equivalents) were dissolved in dichloromethane (15 mL). A 40% aqueous solution of sodium hydroxide(15 mL) were added to this mixture and stirred overnight in the dark.The organic layer was then separated, washed with water (3x10 mL), dried on anhydrous $MgSO_4$, filtered and organic solvent removed in vacuo. The precipitate thus obtained was recrystallised from ethylacetate-hexane furnished the triazole **4** as colorless crystals, yield 80%, m.p.=200-202 ^{0}C (lit. 203-205 ^{0}C). ^{1}H-NMR ($CDCl_3$) δ : 2.30 (3H, s, Me),

2.85(3H, s,Me), 7.20 (2H, d, J=8.5), 7.63 (2H, ddd, J=8.5, 6.4 and 1.0),. 7.80 (2H, ddd, J=8.7, 6.4 and 1.2) 8.70 (2H, d, J=8.7). ^{13}C-NMR ($CDCl_3$) δ : 9. 50, 29.00, 122.00, 123.00, 129.00, 130.00, 130.80, 135.00, 143.00, 143.20, 150.00, 194.30

9-(5-Amino-4-cyano-1,2,3-triazol-1-yl)acridine. 9-Azidoacridine (220 mg, 1.00 mmol), malononitrile (73mg, 1.1 mmol), and tetrabutylammonium bromide (1.00 molar equivalents) were dissolved in dichloromethane (25 mL). A 40% aqueous solution of sodium hydroxide(25 mL) were added to this mixture and stirred overnight in the dark.The suspension was filtered and the residue was washed with water and ethanol. the resulting yellow powder was purified by column chromatography on silica gel. Using hexane-diethyl ether (1:2) as eluent, small amounts of impurities were separated. The fraction from diethyl ether furnised the triazole as a lemon yellow powder. Yield 60%. m.p = 249-251(lit. m.p.= 248-250. ^{1}H-NMR, (DMSO-d_6), δ : 7.32 (2H, br, s, NH_2), 7.50 (2H, d, J=8.55), 7.70 (2H, ddd, J=8.6, 6.6, 1.0), 8.00 (2H, ddd, J=8.70, 6.6, 1.2), 8.35 (2H, d, J=8.6). ^{13}C-NMR (DMSO-d_6),δ : 101,00, 113.80, 122.73, 122.70, 129.00, 129,70, 131.00, 134.35, 149.30, 151.00.

9-(5-Amino-4-phenyl-1,2,3-triazol-1-yl)acridine. 9-Azidoacridine (220 mg, 1.00 mmol), phenylacetonitrile (1.17g, 10 mmol), and tetrabutylammonium bromide (1.00 molar equivalents) were dissolved in dichloromethane (15 mL). A 40% aqueous solution of sodium hydroxide were added to this mixture and stirred overnight in the dark. The precipitate was collected and washed with water and hot methanol to give the triazolylacridine as a bright yellow powder. Yield 90%, m.p.=206-208 ^{0} C(lit.m.p.= 207-209 ^{0}C).^{1}H-NMR, (DMSO-d_6), δ: 6.10 (2H, br s, NH_2), 7.35(1H, tt, J=7.4, 1.20), 7.43-7.52(4H,m), 7.70 (2H, ddd, J=8.7,6.6, 1.1), 7.90-8.00 (4H,m), 7.70 (2H, ddd, J=8.6,1.2, 1.0), 7.90-8.01 (4H, m), 8.35 (2H, ddd, J=8..5, 1.2, 1.0). ^{13}C-NMR, (DMSO-d_6) δ : 123.00, 123.10, 125.00, 126.00, 126.50, 128.40, 129.00, 129.80, 131.10, 132.10, 135.120, 142.40, 149.50.

9-[5-Amino-4-(4-chlorophenyl)1,2,3-triazol-1-yl]acridine. The compound was prepared as above using o-chlorophenylacetonitrile (10.0 mmol) and was obtained as a yellow crystalline powder. Yield =85%, m.p.= 165-167 ^{0} C (lit. m.p.= 167-179 ^{0}C). ^{1}H-NMR, (DMSO-d_6), δ: 5.90 (2H, br s, NH_2), 7.50-7.68 (5H, m), 7.70-7.80 (3H,m), 7.90 (2H, ddd, J=8.6, 6.7, 1.3), 8.40 (2H,d, J=8.6). ^{13}C-NMR, (DMSO-d_6), δ: 123.oo, 123.45, 124.80, 127.50, 128.45, 129.50, 130.00, 150.50, 131.20, 132.40, 133.40, 136.20, 143.60, 149,40.

9-[5-Amino-4-(piperidin-1-ylcarbamoyl)1,2,3-triazol-1-yl]acridine. 9-Azido- acridine (220mg, 1.00 mmol), 2-cyanoacetylpiperidine (167g, 1.10 mmol), and tetrabutylammonium bromide (1.00 molar equivalents) were dissolved in dichloromethane(15 mL). A 40% aqueous solution of sodium hydroxide were added to this mixture and stirred overnight in the dark. The precipitate was collected and washed with water and hot methanol to give the triazolylacridine

as a yellow powder. Yield 50%, m.p.=231-233 ^{0}C(lit.m.p.= 230-232 ^{0}C).^{1}H-NMR, (DMSO-d_6), δ: 1.70 (6H, br), 4.10 (4H, br), 6.50 (2H, d, J=9.0), 7.55 (2H, d, J=8.8), 7.70 (2H, ddd, J= 8.5, 6.6, 1.3), 8.00 (2H, ddd, J= 8.8, 6.6, 1.5), 8.40 (2H, d, J=8.8). ^{13}C-NMR, (DMSO-d_6), δ: 25.50, 25.90, 122.60, 128.00, 129.50, 130.80.

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