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Graphical Abstract

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Direct and Facile Synthesis of 9-Aminoacridine and Acridin-9-yl-ureas

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ABSTRACT

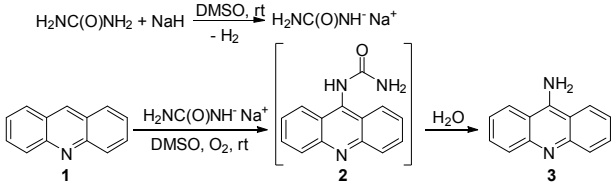
The ability of urea anions to react as nucleophiles with acridine has been investigated. An effective SNH synthesis of 9-aminoacridine was developed using the urea/NaH/DMSO system. However, when mono substituted ureas containing bulky substituents or 1,1-dialkyl substituted ureas were used, products of the SNH reaction of alkyl carbamoyl amination were obtained. Single crystal structure and the tautomerism of selected compound were studied.

The extensive use of acridines in medical sciences has been stimulated by their pharmaceutical properties. Initially, they were shown to have antibacterial,[1a] trypanocidal,[1b] or antimalarial[1c] activities amongst other properties.[1d,e] Later, the high antitumor potency of acridines has also been reported.[1f] The anticancer activity of acridine derivatives is a result of their capacity to interact with nucleic acids.[2] In many cases acridines, demonstrating anticancer properties, have a substituted amino group at position 9 and the nature of the substituent has proven to be important for biological activity.[3] The anticancer activity of 9-aminoacridine derivatives was confirmed *in vitro*, as well as *in vivo* for selected molecules.[4]

9-Amino acridines have been synthesized using multi-step reactions, the final stage of which was the nucleophilic substitution of chlorine or another nucleofuge in position 9 of the acridine molecule (S_NAr reaction).[5] In whole, the nucleophilic aromatic substitution of hydrogen (S_N^H) is well known for the acridine series but examples of reactions with *N*-nucleophiles are still rare. According to a communication by Bauer and co-workers,[6a] acridine readily undergoes the Chichibabin reaction to form 9-aminoacridine in 72% yield upon reaction with sodium amide in dimethylaniline (DMA) at 150 °C. However, in an attempt to reproduce this experiment, the authors[6b] obtained a different result which resulted in the isolation of three compounds - the starting acridine (14%), 9-aminoacridine (31%), and 9,9'-diacridanyl. Recent work[6c] has shown that solvent-free Chichibabin reaction conditions in melted acridine led to the same result.

Recently, we developed a novel approach for the introduction of an amino group or urea moiety to the 1,3,7-triazapyrene molecule.[7] In the course of this study and taking into account the biological significance of amino acridines, we became interested to test the possibility for S_N^H amination and carbamoyl amination reactions of this heterocycle using urea anions as nucleophilic reagents.

At first, we studied the reaction of acridine **1** with urea. As in the previous work,[7] the process was carried out in anhydrous DMSO without isolation from oxygen. The reaction proceeded readily in DMSO at room temperature *via* reaction of the urea anion with the heterocycle to form, after addition of water, 9-aminoacridine **3** in 78% yield (Scheme 1).[8]

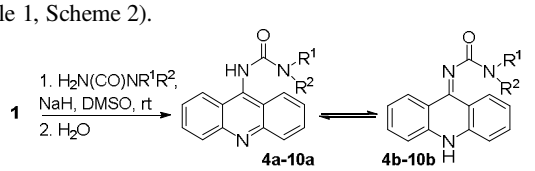


Scheme 1. S_N^H-Amination of acridine **1** by the urea anion.

The reaction progresses according to Scheme 1, with the unstable intermediate acridin-9-yl-urea **2** undergoing conversion into amine **3** in accordance with the previously reported pathway,[7] including deprotonation of the NH_2 group and subsequent elimination of the 9-aminoacridine anion as a leaving group. Addition of water to the reaction mixture leads to protonation of this anion to form product **3**. To confirm that oxygen was the oxidant for this reaction we performed the reaction in DMSO under an argon atmosphere. In this case only traces of product **3** were detected by TLC. Moreover a mixture of oligomerization products was obtained while the starting acridine reacted completely under these conditions. Thus, it is obvious that acridine itself is not an effective acceptor of a hydride ion and the decisive factor for the subsequent aromatization of the σ^H-adduct is access to oxygen.

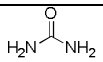
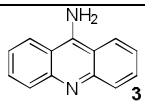
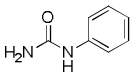
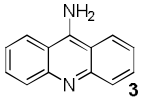
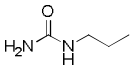
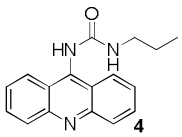
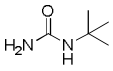
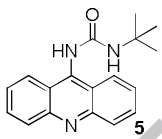
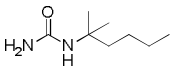
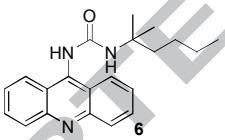
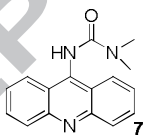
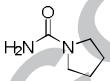
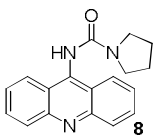
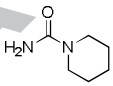
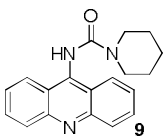
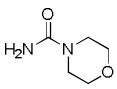
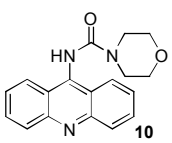
The use of phenyl urea in the reaction with acridine **1** led to same primary amine **3** in 74% yield. Further results were

obtained using mono substituted ureas, such as propyl-urea, *tert*-butyl-urea and (1,1-dimethyl-pentyl)-urea. The anions of these reagents readily reacted with acridine under the same conditions to form the products of nucleophilic substitution of hydrogen in the acridine moiety by the alkyl carbamoyl amino groups - 1-acridin-9-yl-3-propyl-urea **4**, 1-acridin-9-yl-3-*tert*-butyl-urea **5** and 1-acridin-9-yl-3-(1,1-dimethyl-pentyl)-urea **6**, respectively (Table 1, Scheme 2).



Scheme 2. Reaction of acridine **1** with mono alkyl ureas and 1,1-disubstituted ureas at room temperature.

Table 1. Synthesis of 9-aminoacridine and acridin-9-yl-ureas[a]

Entry	Urea	Product	Yield (%)
1		 **3**	78
2		 **3**	74
3		 **4**	78
4		 **5**	67
5		 **6**	67
6		 **7**	89
7		 **8**	84
8		 **9**	84
9		 **10**	82

[a]In all experiments, the use of urea (6 equiv.) and NaH (6 equiv.) was found to be optimal.

In contrast to intermediate **2** (Scheme 1) compounds **4-6** proved to be more stable. The probable cause of their comparative stability is spatial interference in the deprotonation of the NHR groups which is necessary for further conversion. It could be assumed that 1,1-disubstituted ureas also give rise to the products of dialkyl carbamoyl amination. Indeed, when the anions of 1,1-dimethylurea or amides of pyrrolidine-1-carboxylic acid, piperidine-1-carboxylic acid and morpholine-4-carboxylic acid were reacted with acridine under the same conditions, 3-(acridin-9-yl)-1,1-dimethyl-urea **7**, pyrrolidine-1-carboxylic acid (acridin-9-yl)-amide **8**, piperidine-1-carboxylic acid (acridin-9-yl)-amide **9** and morpholine-4-carboxylic acid (acridin-9-yl)-amide **10** were obtained, respectively, in 82-89% yields (Table 1, Scheme 2).

Compounds **4-6** have a doubled set of ^{1}H and ^{13}C signals in the NMR spectra in DMSO-d_6. Undoubtedly these compounds represent novel examples of the known prototropic tautomeric equilibrium of the "aminoacridine - acridanimine" type[9] and exist in DMSO solutions as an equilibrium system of tautomers **a** and **b** in an approximately 1:1 ratio (Fig. 1). Increasing the temperature of the mixture of tautomers **5a**,**b** in DMSO-d_6 to 70 °C did not lead to coalescence of the proton signals in the ^{1}H NMR spectrum; only their broadening was observed to some extent. Further temperature increases led to decomposition. On the other hand, the addition of a small amount of trifluoroacetic acid to the solution in DMSO-d_6 led to a simplification of the spectrum, since both tautomers after protonation give the same cation in which a positive charge is delocalized between the two nitrogen atoms.

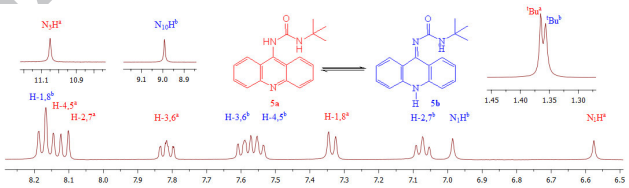
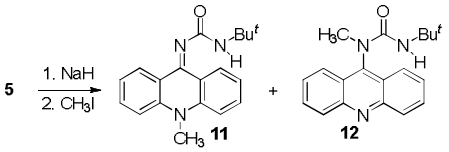


Figure 1. ^{1}H NMR spectrum of the tautomeric equilibrium for 1-acridin-9-yl-3-*tert*-butyl-urea **5** in DMSO-d_6.

To perform the assignment of all ^{1}H NMR signals of tautomers **5a** and **5b** we attempted to synthesize their fixed *N*-methylated forms. Reaction of the ambident anion of compound **5**, generated *in situ* by reaction of NaH with methyl iodide in anhydrous acetonitrile, proceeded unselectively at room temperature to form a mixture of both model compounds: 1-*tert*-butyl-3-(10-methyl-10*H*-acridin-9-ylidene)-urea (**11**, 26%) and 1-acridin-9-yl-3-*tert*-butyl-1-methyl-urea (**12**, 51%) (Scheme 3).[10]



Scheme 3. Synthesis of the fixed *N*-methylated analogs of tautomers **5a** and **5b**.

Proton and carbon assignments in the NMR spectra of compounds **11** and **12** were made on the basis of COSY, NOESY, HSQC and HMBC experiments. In turn we were able to assign all ^{1}H signals in the NMR spectra of tautomers **5a** and **5b**. The structure of compound **5** was also confirmed by single crystal X-ray determination. It is noteworthy that the crystal obtained from low-polarity chloroform had in the unit cell both tautomeric forms **5a** and **5b** which were connected by an

intermolecular hydrogen bond (Fig. 2).[11] However, the crystal grown by slow evaporation from more polar ethyl acetate existed only as 1-acridin-9-yl-3-*tert*-butyl-urea (tautomer **5a**).[12] The single crystal X-ray data show that the dihydroacridine fragment of compound **5b** was not planar and the angle between the planes of the two benzene rings was 7.63°.

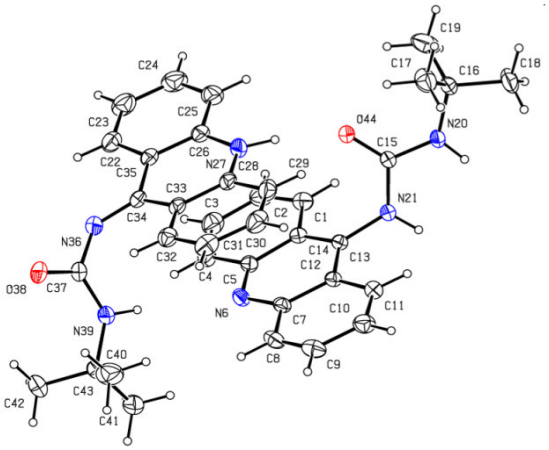


Figure 2. ORTEP diagram of compounds **5a,b**.

In contrast to products **4-6** the tautomeric equilibrium for compounds **7-10** in DMSO was almost completely shifted towards one tautomer. To identify in which form they existed in DMSO, COSY, NOESY, HSQC and HMBC NMR experiments were performed. As it turned out, their preferred tautomeric forms were imino forms **7b-10b**. This was in accordance with the observation[9a] that any hindrance for free rotation around the C_9-N bond in 9-alkylaminoacridines makes the imino form more preferable.

A distinctive feature of the ^{1}H NMR spectrum of compound **7** was the magnetic nonequivalence of the *N*-methyl groups which gave two proton singlets at 2.82 and 3.01 ppm, i.e. they are separated by 76 Hz. In the ^{13}C NMR spectrum there were also two carbon signals. A similar phenomenon was observed in the NMR spectra of compounds **8-10**, where individual signals were formed from the α-methylene groups at the nitrogen atom as well as the β-methylene groups. This may be explained in at least two ways: (i) the known restricted rotation about the C-N bond for amides or (ii) the influence of the magnetic field of the benzene ring in the region of these substituents.

Compounds **4-10** were unstable upon heating in the crystalline state as well as in solution and upon slow heating gradually change color and eventually melt at the melting point of 9-aminoacridine **3**.

In conclusion, the advantages of the described method for the synthesis of 9-aminoacridine and acridin-9-yl-ureas include reagent availability, experimental simplicity and its applicability to the synthesis of a broad range of 9-amino substituted acridines. The crystal structure and tautomerism of selected compounds were investigated.

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8. *General procedure*: To a solution of the corresponding urea (3 mmol) in anhydrous dimethyl sulfoxide (5 mL), sodium hydride (3 mmol, based on active ingredient) was added at room temperature. When hydrogen bubbling ceased, acridine (0.5 mmol) was added. The mixture was stirred vigorously at room temperature for 24 h. Then water (30 mL) was added and the precipitate was filtered off, washed with water and dried. Compounds **3, 7** and **10** were purified by recrystallization from the appropriate solvents (see ESI). Product **6** was additionally washed with hot water on the filter (~70 °C; 40 mL) during isolation to remove excess starting materials and the dry product was recrystallized from a mixture of dichloromethane and petroleum-ether. Compound **5** was purified by silica gel flash chromatography, eluting with a 5:1 mixture of benzene-EtOAc (colorless fraction) and then with EtOAc (yellow fraction). The first fraction containing the starting materials was discarded; product **5** was obtained from the second fraction after solvent evaporation.
   Data for 9-aminoacridine (**3**): yellow solid (76 mg, 78% upon use urea and 72 mg, 74%, using phenyl urea); mp 232-233 °C (EtOAc). Lit[6b] mp 233-234 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (2H, br. d, J = 8.4 Hz, H-1,8); 7.81 (2H, br. d, J = 8.5 Hz, H-4,5); 7.77 (2H, br. s, NH_2); 7.64 (2H, ddd, J = 8.5 Hz, J = 8.0 Hz, J = 1.0 Hz, H-3,6); 7.31 (2H, ddd, J = 8.4 Hz, J = 8.0 Hz, J = 1.0 Hz, H-2,7). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.1; 148.8; 129.8; 128.7; 123.3; 121.5; 112.9. IR (thin film) 3342, 3181, 1649, 1613, 1562 cm^{-1}. ESI-HRMS: calcd for $C_{13}H_{11}N_2$ $[M+H]^+$ 195.0917, found 195.0919.
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10. *Procedure for the synthesis of 1-tert-butyl-3-(10-methyl-10H-acridin-9-ylidene)-urea (**11**) and 1-(acridin-9-yl)-3-tert-butyl-1-methyl-urea (**12**).* To a solution of 1-acridin-9-yl-3-*tert*-butyl-urea (**5**; 147 mg, 0.5 mmol) in anhydrous acetonitrile (5 mL), sodium hydride (20 mg, 0.5 mmol, based on active ingredient) was added at room temperature. After stirring for 0.5 h methyl iodide (71 mg, 0.5 mmol) was added and the mixture was stirred for 1.5 hours at room temperature. Then water (20 mL) was added and the precipitate was filtered off, washed with water and dried.

Separation of the isomers was performed using dry silica gel flash chromatography, eluting with benzene-EtOAc 5:1 (colorless fraction) and then with ethyl acetate (yellow fraction). From the first fraction compound **12** was obtained and from the second product **11** was isolated.

Data for 1-*tert*-butyl-3-(10-methyl-10*H*-acridin-9-ylidene)-urea (**11**): maize yellow solid (40 mg, 26%); mp 182-183°C (CH_2Cl_2 with petr.-ether; with dec.). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (2H, d, *J* = 8.4 Hz, *H*-1,8); 7.64 (2H, br. t, *J* = 7.6 Hz, *H*-3,6); 7.59 (2H, d, *J* = 8.4 Hz, *H*-4,5); 7.16 (2H, br. t, *J* = 7.2 Hz, *H*-2,7); 7.00 (1H, s, N_1H); 3.75 (3H, s, NCH_3); 1.32 (9H, s, $C(CH_3)_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0 (*C*O); 151.4 (*C*-9); 141.4 (*C*-4a,10a); 132.2 (*C*-3,6); 126.9 (*C*-1,8); 120.5 (*C*-2,7); 120.0 (*C*-8a,9a); 115.2 (*C*-4,5); 49.8 ($C(CH_3)_3$); 34.1 (NCH_3); 28.7 ($C(CH_3)_3$). IR (thin film): 3340, 3271, 3065, 2960, 1637, 1569 cm^{-1}. ESI-HRMS: calcd for $C_{19}H_{22}N_3O$ $[M+H]^+$ 308.1757, found 308.1775.

11. CCDC 1472661 (**5a, 5b**) contains the crystallographic data for the crystal from chloroform for this manuscript.
12. CCDC 1465304 (**5a**) contains the supplementary crystallographic data for the crystal from ethyl acetate for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at…

- C-N bond formation by direct oxidative nucleophilic substitution of hydrogen
- A new approach to synthesize 9-aminoacridine
- A new synthesis of 1-(acridin-9-yl)-3-alkyl(dialkyl)-ureas has been developed