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Synthesis of 6-Amino-3,4-dihydroisoquinolinium Derivatives by Ring-Opening Reactions of Acridizinium Ions

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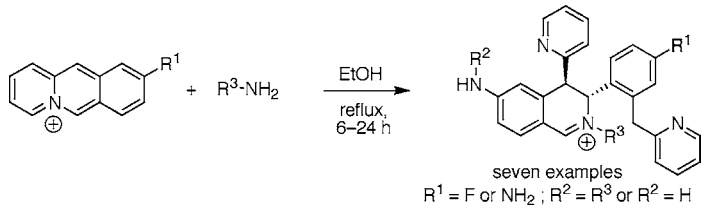
ABSTRACT



The reaction of the 9-fluoroacridizinium (9-fluorobenzo[*b*]quinolizinium) or the 9-aminoacridizinium (9-aminobenzo[*b*]quinolizinium) ion with primary alkyl amines gives with high diastereoselectivity 6-amino-3,4-dihydroisoquinolinium derivatives as main products, which exhibit pronounced absorption and fluorescence properties. It is proposed that the reaction proceeds via a nucleophilic ring-opening followed by an aza Diels–Alder reaction.

Isoquinoline derivatives are naturally occurring alkaloids and promising lead structures in drug discovery.[1] Therefore, several methods to synthesize derivatives of isoquinoline, or 1,2-dihydro- and 1,2,3,4-tetrahydroisoquinoline derivatives have been reported.[2] In addition, *N*-alkylated isoquinolinium compounds with biological activity have been identified recently.[3] Although several synthetic routes to isoquinolinium derivatives are known,[2] relatively few studies have been reported on the synthesis and investigation of 3,4-dihydroisoquinolinium ions. In most cases, rather simple structures are obtained by *N*-alkylation of the corresponding isoquinoline precursor. The resulting products are usally applied as substrates for subsequent reactions, such as 1,3-dipolar cycloadditions,[4] addition reactions,[5] or oxidation reactions.[6] Herein, we report the unexpected synthesis of 4-pyridyl-3,4-dihydroisoquinolinium derivatives by the reaction of acridizinium (benzo[*b*]quinolizinium) ions with primary alkylamines.

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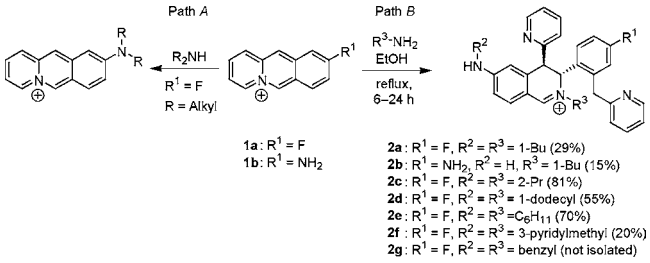
During our studies on the synthesis of *N*-substituted 9-aminoacridizinium derivatives by nuclecophilic substitution reactions of the corresponding 9-fluoroacridizinium ion (**1a**), we discovered that the substituted 9-aminoacridizinium derivative was the main reaction product when a secondary aliphatic amine or a substituted aniline was used as reactant (Scheme 1, path A).[7] However, when primary alkyl amines

Scheme 1. Synthesis of 3,4-Dihydroisoquinolinium Derivatives



were made to react with the salt **1a** at similar conditions, the *N*-substituted 9-aminoacridizinium derivative was formed in very low yields, i.e., less than 5%,[7b] whereas another product was formed in significant amounts. Thus, the reaction of 9-fluoroacridizinium (**1a**) with 2 molar equiv of *n*-butylamine gave a major product, which was readily separated by chromatography and whose ^{1}H NMR and ^{13}C NMR data revealed a partially saturated bicyclic heterocycle instead of the expected tricyclic acridizinium unit. Eventually, X-ray diffraction analysis of a well-crystallized perchlorate salt, prepared by ion methathesis of the crude product, showed unambiguously that the 3,4-dihydroisoquinolinium derivative **2a** was formed as the main product (Figure 1). This structural assignment is consistent with the one- and two-dimensional ^{1}H NMR spectroscopic analysis, mass-spectrometric data, and combustion analysis (cf. Supporting Information). Especially characteristic of the 3,4-dihydroisoquinolinium structure are the singlet of the iminium proton H-1 (δ = 8.99 in acetone-d_6) and the signals of the protons H-3 (δ = 6.48) and H-4 (δ = 4.84), which appear as slightly broadened singlets due to a very small spin−spin coupling constant, in agreeement with a dihedral angle between these protons of 79°, as observed from the X-ray diffraction data, and the ^{1}H NMR data of related 3,4-dihydroisoquinolinium ions.[8] Notably, the product **2a** is formed with high diastereoselectivity, i.e., the substituents at C3 and C4 have an *anti* configuration, as clearly indicated by the stucture in the

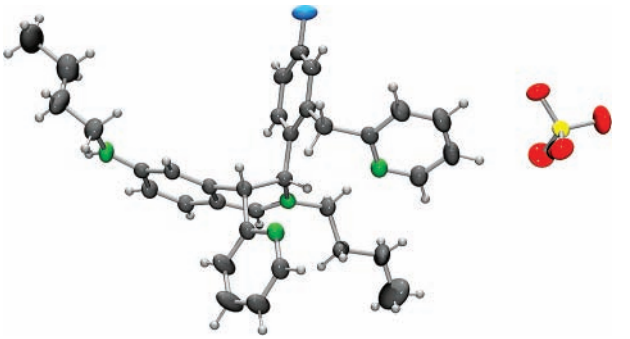


Figure 1. Structure of 3,4-dihydroisoquinolinium derivative **2a** $\cdot$ **ClO$_4$** in the solid state as derived from X-ray diffraction analysis. The thermal ellipsoids for non-H atoms are shown with 50% probability (gray: C; white: H; green: N; red: O; blue: F; yellow: Cl).

solid state (Figure 1) and by only one set of NMR signals, even in the crude product.

To assess whether the 3,4-dihydroisoquinolinium structure is generally formed in the reaction of aliphatic amines with the fluoroacridizinium ion **2a**, we extended the study to several selected amines (Scheme 1, path B). The reaction of compound **1a** with cyclohexylamine, isopropylamine, *n*-dodecylamine, and 3-aminomethylpyridine gave the corresponding dihydroisoquinolinium derivatives **2c**−**f** in moderate to low yields. With benzylamine as reagent, the formation of the dihydroisoquinolinium **2g** was indicated by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (40−50% yield), but the product could not be isolated by chromatography and/or crystallization in analytically pure form. When *tert*-butylamine was employed as nucleophile, the corresponding dihydroisoquinolinium could not be detected from the reaction mixture, indicating that the reaction is sensitive toward steric interactions between the substrate and the nucelophile. Finally, with a donor-substituted acridizinium ion such as the 9-aminoacridizinium (**1b**), the same reaction may be performed, i.e., the reaction with *n*-butylamine gave the corresponding isoquinolinium derivative **2b** in 15% yield.

The formation of the 3,4-dihydroisoquinolinium ions **2** may be explained by an initial nucleophilic ring-opening, followed by an aza (imino) Diels−Alder reaction[9] of the intermediates, and subsequent nucleophilic aromatic substitution of the fluorine atom (Scheme 2). Considering the reactivity of position 6 of the acridizinium ion toward nucleophiles,[10] the formation of derivatives **2a**−**g** is likely to be induced by the addition of the amine to the acridizinium ion **1a** and a subsequent electrocyclic ring-opening reaction

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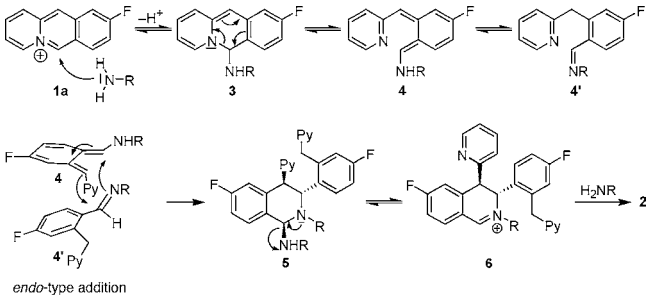
Scheme 2. Proposed Mechanism for the Formation of Dihydroisoquinolinium Derivatives **2** by the Reaction of Primary Amines with 9-Fluoroacridizinium (**1a**)



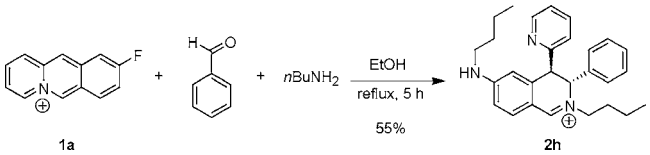
to give the intermediate **4**, which exists in a tautomeric equilibrium with the pyridylmethylbenzaldimine **4′**. The imine **4′** (R = alkyl) may then react in a Diels−Alder-type reaction with the tautomeric enamine **4**, which adopts the *cis*−*trans* configuration preferentially due to steric repulsion between the amino and the pyridyl substituent. The resulting tetrahydroisoquinoline **5** is transformed to the dihydroisoquinolinium **6** by the elimination of amine. A subsequent nucleophilic aromatic substitution of the fluorine atom in the isoquinolinium system with excess amine eventually yields the final product **2**. It should be noted that the ring-closure to give the isoquinolinium **5** may also take place in a stepwise process rather than in a concerted reaction. Although it is difficult to obtain unambiguous experimental support to distinguish between the two mechanisms, the proposed aza Diels−Alder pathway is in agreement with several known synthetic routes to nitrogen-containing heterocycles.[8,9]

The corresponding imine **4′** could not be isolated under the reaction conditions, probably due to a rapid subsequent reaction. Nevertheless, it has been shown for the parent acridizinium and methyl-substituted derivatives that the reaction with nitrogen nucleophiles yields the corresponding (2-pyridylmethyl)benzcarbaldimine derivatives; however, the formation of dihydroisoquinolinium ions was not observed.[10c] Additional supporting evidence for the proposed formation of the intermediate imine was provided by the isolation of the aldoxime **4′** (R = OH) that is formed in the reaction of **1a** with hydroxylamine (cf. Supporting Information).

Moreover, the reaction of *n*-butylamine and **1a** in the presence of an excess of benzaldehyde gives the dihydroisoquinolinium **2h** (Scheme 3).[11] This observation is consistent with the proposed imine intermediate, because under these conditions the formation of the corresponding benzaldimine is most likely. Moreover, this result demonstrates that in the presence of excess aldehyde, the reaction provides a general access to 3-aryl-4-pyridyl-dihydroisoquinolinium derivatives. The proposed aza Diels−Alder cycloaddition between the imine **4′** and the diene **4** would explain the high diastereoselectivity of the product formation, because the steric repulsion of the aryl substituent of the imine and the pyridyl

(11) With ethanal as aldehyde, the reaction did not take place, presumably because the intermediate enolate interferes with the reaction.

Scheme 3. Synthesis of 3-Aryl-4-pyridyl-substituted Dihydroisoquinolinium Derivatives



substituent of the diene as well as additional attractive secondary orbital interactions are likely to result in an *endo*-type addition (Scheme 2) to give the *anti* configuration of the C3 and C4 substituents. Such a diastereoselectivity was also observed in the synthesis of dihydroisoquinolinium derivatives by a cycloaddition reaction of benzo[*c*]pyrylium salts with substituted benzaldimines,[8] which represents another example of a direct access to the dihydroisoquionlinium system by the aza Diels−Alder reaction.

Finally, the proposed mechanism also explains the preferential formation of *N*-substituted 9-aminoacridizinium ions upon reaction of 9-fluoroacridizinium (**1a**) with *secondary* aliphatic amines.[7b] In the latter case, the corresponding intermediate **4**, even if it is formed at the reaction conditions (as indicated by the dark coloration of the reaction medium), cannot form a tautomer **4′**, thus preventing the sequential steps which lead to the formation of the dihydroisoquinolinium product.

Considering the π-conjugation between the amino substituent and the endocyclic iminium functionality, the 6-amino-3,4-dihydroisoquinolinium ions **2** resemble the structure of polymethine dyes, which are among the most versatile functional dyes.[12] Interestingly, only a few 6-amino-3,4-dihydroisoquinolinium derivatives are reported[13] and little is known about their electronic absorption and emission properties. Nevertheless, it may be proposed that, in the same way as the aminoquinolinium derivatives,[14] the 6-amino-3,4-dihydroisoquinolinium derivatives exhibit a high potential to be used as fluorescent probes. Therefore, we investigated the photophysical properties of the cyclohexyl-substituted derivative **2e** as a representative example (Table 1). The

Table 1. Absorption and Emission Properties of **2e** in Different Solvents

solvent[a]	λ_{abs}/nm[b]	$\epsilon/10^4$ M^{-1} cm^{-1}	λ_{em}/nm[c]	ϕ_f[d]
H_2O	411	3.96	449	0.13
CH_3OH	412	4.57	448	0.18
EtOH	414	4.55	447	0.25
2-PrOH	415	4.61	447	0.33
CH_3CN	400	4.49	445	0.21
DMSO	412	4.43	450	0.23
CH_2Cl_2	413	4.31	440	0.60
$CHCl_3$	405	4.18	451	0.33
THF	407	3.82	449	0.29

[a] In order of decreasing $E_T(30)$ values. [b] Long-wavelength absorption maximum, c(**2e**) = 5.0 × 10^{-5} M. [c] Emission maximum, c(**2e**) = 1.0 × 10^{-5} M; excitation wavelength, λ_{ex} = 410 nm. [d] Fluorescence quantum yield, measured relative to Coumarin 153 (ϕ_f = 0.38, c = 1.0 × 10^{-5} M in EtOH).

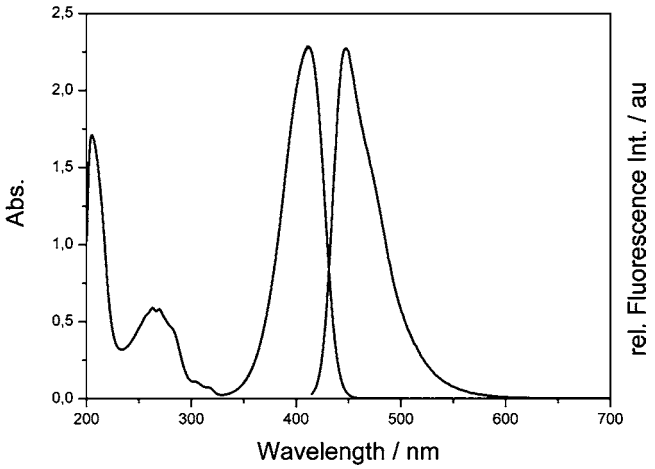


Figure 2. Absorption and emission spectrum of the 6-amino-3,4-dihydroisoquinolinium derivative **2e** in methanol (absorption spectrum: $c = 5 \times 10^{-5}$ M; emission spectrum: $c = 10^{-5}$ M).

absorption and emission spectra of **2e** in methanol are shown in Figure 2. Such as in the case of aminoquinolinium[14] and aminoacridizinium derivatives,[15] the 3,4-dihydroisoquinolinium ions exhibit only a marginal solvatochromism. The aminoisoquinolinium derivative **2e** has a relatively strong long-wavelength absorption band with maxima ranging from 400 nm (in CH_3CN) to 415 nm (in 2-PrOH) and emission maxima between 440 (in CH_2Cl_2) and 451 nm (in $CHCl_3$), with emission quantum yields from approximately 0.10 to 0.60.[16] The Stokes shift of derivative **2e** varies from 1725 cm^{-1} (2-PrOH) to 2518 cm^{-1} ($CHCl_3$).

In summary, we have discovered an unexpected access to 6-amino-3,4-dihydroisoquinolinium derivatives starting from easily available acridizinium ions. These compounds exhibit promising absorption and emission properties and may be further investigated as potential fluorescent probes.

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Supporting Information Available: Synthetic procedures; full characterization and ^1H and ^{13}C NMR spectra of all new compounds; crystallographic data of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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