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Novel approach to synthesis of substituted 3-aminoquinolines from nitroarenes and protected ethyl aminocrotonate

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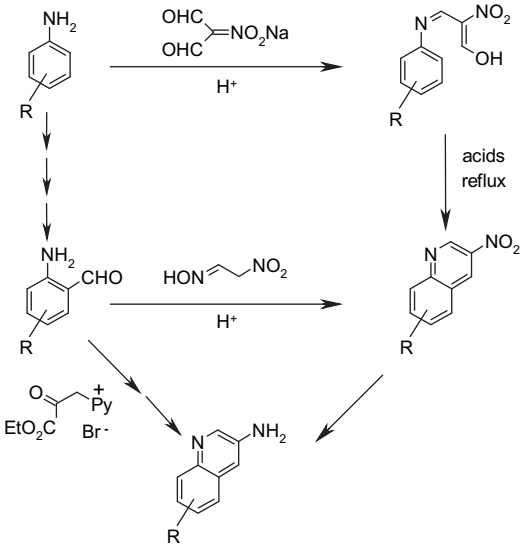
ABSTRACT

The addition of mono- and dianions of ethyl *N*-pivaloyl-3-aminocrotonate to substituted nitroarenes, followed by action of silylating or acylating agent, leads to 3-aminoquinoline carboxylic acid derivatives. Hydrolysis and decarboxylation of the latter, carried out efficiently under relatively mild conditions, afford 3-aminoquinolines diversely substituted in the benzo-fused ring.

1. Introduction

3-Aminoquinolines are frequently employed in synthesis and modifications of a variety of potentially biologically active compounds.[1] In particular, 3-aminoquinoline terminated dipeptides have been found to exhibit interesting pharmacological properties.[1a–c] Taking part in a project directed towards compounds of similar structure and of potential biological activity, we were required to synthesize 3-aminoquinolines bearing numerous different substituents, such as Cl, Br, F, CF_3 and others, in the benzo-fused ring. Literature reports on synthesis of such derivatives, which have no additional substituents in the heterocyclic part of the molecule, or have such substituents, which could be easily removed, are rare. A majority of them are based upon the reduction of the corresponding 3-nitroquinolines. Preparation of the latter can be accomplished by nitration of the quinoline ring, or much more conveniently and regioselectively, by construction of the heterocyclic ring on substituted aniline derivative.[2] The latter approach involves two pathways (Scheme 1). The first one is based on a two-step condensation of the appropriate aniline with the sodium salt of nitromalonaldehyde[3]—an explosive compound prepared from mucobromic acid.[4] Although the first step, formation of Schiff bases (anils), is usually efficient, the cyclization step leading to the bicyclic skeleton requires selected conditions of acidic catalysis and produces variable results. The electrophilic character of the reaction limits the whole synthesis to anilines bearing electron-donating substituents.[3b] This method has been applied to preparation of 6-methyl- and 6-methoxy- derivatives of 3-aminoquinolines.[3a,b]



Scheme 1. Common synthetic pathways leading to 3-aminoquinolines.

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Another, more general method, which could be suitable also for electron deficient systems, is the Friedlander-type condensation,[5] which comprises reaction of 2-formylanilines with nitroacetaldehyde oxime (metazonic acid)[6]—a product of self-condensation of nitromethane under basic conditions.[7] The drawback of this method is that the desired 2-formylanilines are usually unstable and their preparation from easily available substrates is difficult.[8–10] Directed metallation of *N*-protected anilines[8] or bromoanilines[9] followed by action of dimethylformamide, and reduction of *ortho*-nitro aryl aldehydes[10] are employed in this respect.

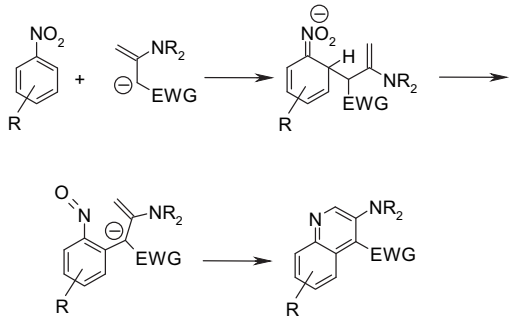
An interesting synthesis of a few substituted 3-aminoquinolines, omitting preparation of corresponding nitroquinolines, comprises condensation of substituted 2-formylanilines with 1-(2-ethoxy carbonyl-2-oxoethyl)pyridinium bromide, which, followed by aminolysis with pyrrolidine, leads to 3-aminoquinoline-2-carboxy lates.[11] In view of possible further decarboxylation of the latter, it can be considered as a potential precursor of the target 3-aminoquinolines. The method, however, also depends on availability of appropriate 2-formylanilines.

The considerations presented above and also attempted preparations of selected target 3-aminoquinolines, carried out according to known schemes, led us to the conclusion, that synthesis of 3-aminoquinolines in general, and particularly those bearing electronwithdrawing groups, is a really demanding task and made us think about an alternative, shorter and/or more effective way of their preparation.

Working for the last decade on synthesis of polycyclic nitrogen compounds we have found that the combination of a base and a Lewis acid promoted multistep reactions of nitroarenes with properly functionalized precursors of allylic anions, leading to various substituted quinolines and other bicyclic heterocycles with a fused pyridine ring.[12] Similar approach was successful also in transformations of nitroarenes—depending on the structure of the nucleophilic agent—into 1-hydroxyindole,[13] 2,1-benzisoxazole[14,15b] or acridine[15,16] systems. The role of the Lewis acid could be played efficiently also by silylating[12a–c,15,16] or acylating agents.[16] Thus we decided to adopt this methodology for synthesis of the title compounds.

2. Results and discussion

As we have found earlier, the reaction of nitroarenes with allylic carbanions leads to a new fused pyridine ring via addition of the more nucleophilic centre of the ambident anion at the *ortho* position with formation of σ^H-adducts, followed by transformation of the nitro group into a nitroso group—promoted by base and Lewis acid, silyl or acyl halide—then completed by condensation of the nitroso function with a side-chain allylic anion. Accordingly, the assumed course of the reaction leading to 3-aminoquinoline derivatives, is depicted on Scheme 2.



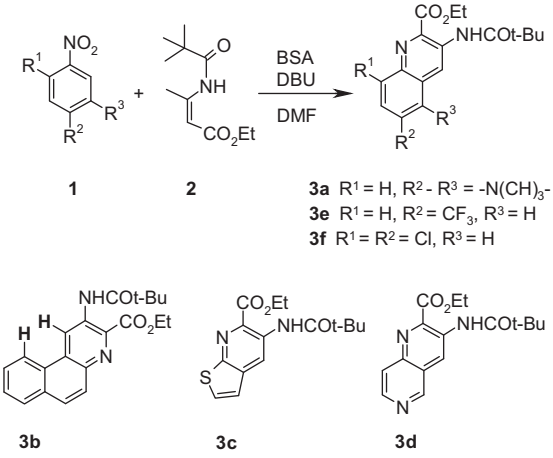
Scheme 2. Projected synthesis of substituted 3-aminoquinoline precursors.

The ester group was chosen for stabilization of the allylic anion, bearing in mind its further removal from the expected cyclization product. In preliminary experiments, commercial and cheap ethyl-3-aminocrotonate was employed.

On the basis of our earlier results, two procedures were examined for the reaction—the so called 'one-pot' procedure[12] and the 'step-by-step' method.[16] The first one consists of mixing the substrates with *N*,*O*-bis-trimethylsilylacetamide (BSA) and DBU in DMF at ambient temperature, for an adequate—usually prolonged—time. In the second procedure, deprotonation of the aminocrotonate with strong base, formation of σ^H-adducts with the nitroarene, its transformation into nitroso compound promoted by pivaloyl chloride and final cyclization—although carried out in the same pot—were time-separated. The process was carried out at −78 °C in order to attain possibly high stability of the intermediate σ^H-adduct.

Unfortunately, for ethyl 3-aminocrotonate treated with nitroarenes such as 4-chloro- and 2,4-dichloronitrobenzene, neither of the above methods led to the desired products. Hence, one can suppose, that protection of the amino function to avoid its deprotonation is necessary to generate the allylic anion. However, attempted reactions of an *N*,*N*-disubstituted derivative, namely ethyl-3-phthalimidocrotonate, were also unsuccessful. On the other hand, *N*-benzoyl and *N*-pivaloyl aminocrotonates gave positive preliminary results, and the latter—more promising—was subjected to the further inspection.

Thus, when ethyl 3-(*N*-pivaloylamino)crotonate[17] **2** was reacted with substituted nitrobenzenes and selected heterocyclic nitroarenes (**1**) under 'one-pot' conditions, the slow reactions led to the 3-aminoquinoline derivatives, but the yields were generally low. Only the more electrophilic 6-nitroquinoline (**1a**) gave the cyclization product in moderate 30% yield, while substituted nitrobenzenes (**1e**,**f**) reacted very poorly (Scheme 3, Table 1).



Scheme 3. One-pot synthesis of precursors of 3-aminoquinolines.

Table 1
One-pot condensation of nitroarenes **1** with **2**

Entry	Nitroarene			**3**	Yield [a]/%
	R1	R2	R3		
1	H	–N(CH)$_3$–		**a**	30
2	H	–(CH)$_4$–		**b**	20
3		[b]		**c**	18
4		[c]		**d**	11
5	H	CF_3	H	**e**	6
6	Cl	Cl	H	**f**	2

[a] Isolated.
[b] 2-Nitrothiophen.
[c] 4-Nitropyridine.