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A Novel Convenient Synthesis of Benzoquinazolines

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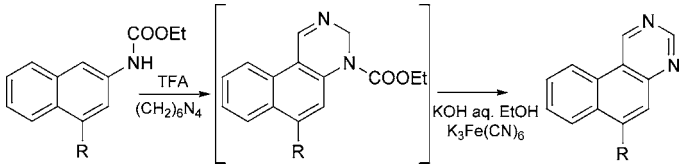
ABSTRACT



A novel synthetic pathway to benzoquinazolines from naphthylamines is reported. Benzoquinazoline nucleus was cyclized in good yield from *N*-protected naphthylamines using hexamethylenetetramine in TFA and potassium ferricyanide in aqueous ethanolic KOH. This method is efficient and convenient with respect to previously reported synthetic pathways.

The pyrimidine ring is often a part of the heterocyclic skeleton of many natural and synthetic products exerting a large variety of biological activity.[1] There are many literature methods for the synthesis of fused pyrimidines, such as quinazoline or benzoquinazoline: all of the synthetic pathways need as starting products aromatic compounds carrying an amino group together with an *ortho* carbonilic carbon (anthranilic derivatives for Niementowski's synthesis[2] and 2-aminoacylbenzene derivatives for Bischler's synthesis[3]) or a methylene carbon (*o*-aminobenzylamine for Riedel's synthesis[4]), and many of these methods suffer from limitations of starting material availability.

Now we have found an efficient and short route to the benzoquinazoline nucleus, consisting of the construction of the entire pyrimidine ring starting from simple aminonaphthalenic compounds using hexamethylenetetramine in TFA, which is a modification[5] of the Duff reaction.[6]

Working with nitrogen heterocyclic compounds in search of new antiproliferative drugs,[7] we used aminonaphthalenes to obtain pyridonaphthalenic or benzoquinazolinic derivatives, which have to be functionalized with known pharmacophoric substituents, such as methanesulfonamidoanilines, e.g., amsacrine.

So, with the aim to introduce a formyl group into 4-bromo-2-naphthylamine on which to further cyclize a pyrimidine nucleus, we have found a novel ring closure of the benzoquinazoline system.

It is well-known that when treating naphthylamines with hexamethylenetetramine in acidic conditions no formylation reaction occurred and only Tröger's bases analogues[8] or their aryltetrahydroquinazoline intermediates[9] are obtained.

After appropriate protection of the amino group with ethyl chloroformiate, refluxing ethyl (4-bromonaphthalen-2-yl)-carbamate (**2a**) in the same way with hexamethylenetetramine in acetic acid led to no reaction. However, when TFA was used instead of acetic acid, we noted the formation of ethyl 6-bromo-3*H*-benzo[*f*]quinazolin-4-carboxylate (**3a**)

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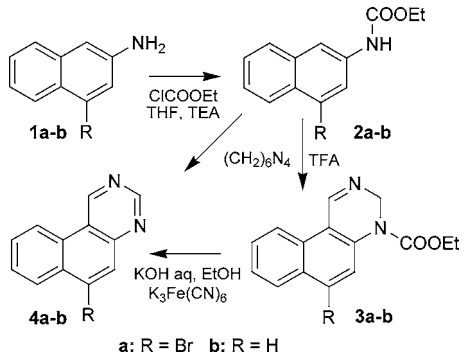
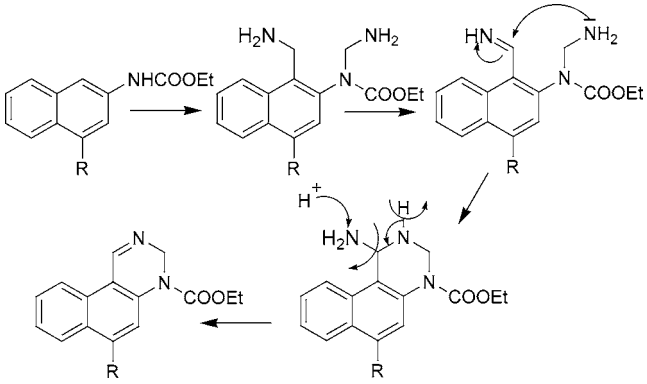
(Scheme 1). Product **3a** was obtained unequivocally with angular geometry, as confirmed by NOESY experiments showing a NOE correlation between H-1 and H-10 (not possible for linear isomer).

Scheme 1



The reaction mechanism probably involves contemporaneous aminomethylation at the *ortho*-position (as described for the Duff reaction)[10] and at the nitrogen atom of the carbamoyl group. The successive dehydrogenation of *o*-aminomethyl to aldimino group promotes an intramolecular cyclization to dihydropyrimidine ring (Scheme 2).

Scheme 2

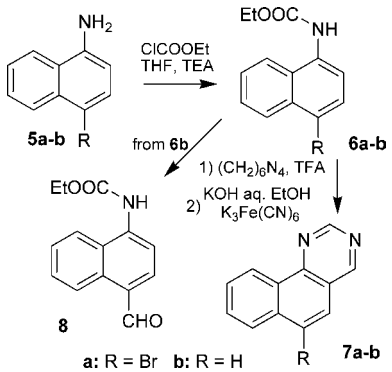


Intermediate **3a** was finally converted to the aromatic 6-bromobenzo[*f*]quinazoline (**4a**) by hydrolizing the carbamoyl function in aqueous ethanolic potassium hydroxide and directly aromatizing the dihydropyrimidine ring with potassium ferricyanide.[11] Compound **4a** was easily obtained in one pot from compound **2a** using the same synthetic protocols without isolating intermediate **3a**, with an increase in the total yield (from 6% to 16%) and a convenient reduction of reaction time and workup.

To verify if this synthetic method could have a widespread application, we performed the reaction on α-naphthylamine without a substituent and on *β*-naphthylamine analogues. When ethyl (naphthalen-2-yl)carbamate (**2b**) was reacted with hexamethylenetetramine in TFA, followed by treatment with aqueous ethanolic potassium hydroxide and potassium ferricyanide, benzo[*f*]quinazoline (**4b**) was obtained in quantitative yield (Scheme 1), so proving the applicability of the method to *β*-naphthylamines.

The reaction protocol was applied also to α-naphthylamines (Scheme 3). After appropriate protection of the amino group, treating ethyl (4-bromonaphthalen-1-yl)carbamate (**6a**) in the same way previously described led to 6-bromobenzo[*h*]quinazoline (**7a**) in moderate yield. On the other hand, from ethyl (naphthalen-1-yl)carbamate (**6b**) compound **8** was obtained in 47% yield and only traces of benzo[*h*]quinazoline (**7b**) were isolated, since with the used reaction conditions typically formylation at the free *para* position preferentially occurred.[5]

Scheme 3



In conclusion, we have found a novel synthetic approach for the synthesis of benzo[*f*]quinazoline and 6-substituted benzo[*h*]quinazoline; this method is efficient and time-saving and uses simple naphthylamines as starting products. Further investigations with different aromatic amines are in progress.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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