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An Efficient and Simple Aminobenzannulation Reaction: Pyrrolidine as a Trigger for the Synthesis of 1-Amino-acridines

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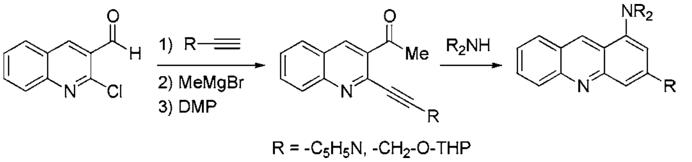
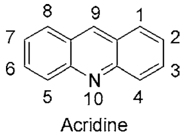
ABSTRACT



A new aminobenzannulation methodology has been developed and applied successfully to the synthesis of 1-amino-acridines. The key and last step goes through an enamine intermediate that was detected in some cases. When pyrrolidine and powdered 4 Å molecular sieves were used, the enamine synthesis and the aminobenzannulation step took place subsequently, whereas for other secondary amines, neutral Al_2O_3 or $PtCl_2$ catalysis was necessary.

Scheme 1. Acridine Structure and Numbering



Acridines are interesting heteroaromatic structures (Scheme 1) that are much sought after targets because of their broad biological properties.[1] Their biological activities against bacteria,[1,2] parasites,[2] or tumors[3] depend mainly on the nature and position of substituents on the acridine nucleus. For these reasons we were interested in finding a method to smoothly construct 1-amino-acridines because of the usual harsh conditions, i.e., high temperature and/or strongly basic or acid media, needed for synthesizing acridines via the known methods: viz. through acridone intermediates,[4,5] the Bernthsen reaction,[6] the cyclization of diphenylamine-2-carboxaldehyde,[7] or by adaptation of the Pfitzinger quinoline synthesis.[8]

Our previous work[9] allowed us to obtain trisubstituted acridines via a 6-*endo-dig* cyclization process (benzannula-

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(4) Atwell, G. J.; Rewcastle, G. W.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1987**, *30*, 664−669.

(5) Sourdon, V.; Mazoyer, S.; Pique V.; Galy, J.-P. *Molecules* **2001**, *6*, 673−682.

(6) Bernthsen, A.; Bender, F. *Chem. Ber.* **1883**, *16*, 1802−1819.

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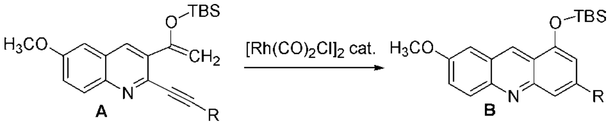
(8) Smolders, R. R.; Waefelaer, A.; Coomans, R.; Francart, D.; Hanuise, J.; Voglet, N. *Bull. Soc. Chim. Belg.* **1982**, *91*, 33−42.

10.1021/ol050380z CCC: $30.25

Scheme 2. Previous Work

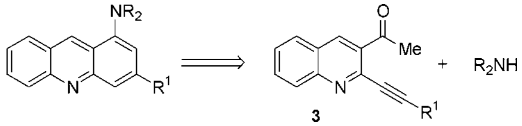


R = $-C_4H_9$, -Ph, $-CH_2$-O-THP, $-CH(OEt)_2$

tion) catalyzed by a rhodium(I) complex (Scheme 2). Benzannulation has been frequently used to construct molecules by different means: transition-metal carbene complexes[10] and metal-catalyzed[11] or metal-free methods.[12]

We were interested in finding an alternative approach to acridines that could directly provide an amino group at position 1 of the acridine moiety. Instead of using the TBS-protected methyl ketone **A** from our previous work[9] (Scheme 2), we dealt with its unprotected precursor **3** (Scheme 3) and a secondary amine (R_2NH), leading to a straightforward aminobenzannulation reaction.

Scheme 3. Aminobenzannulation Reaction



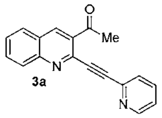
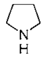
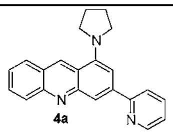
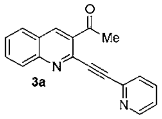
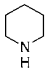
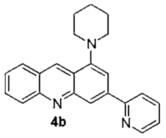
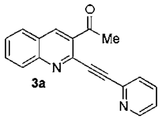
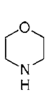
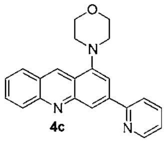
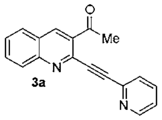
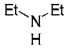
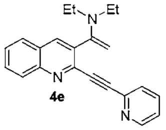
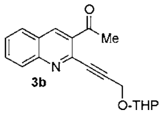
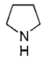
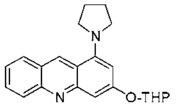
3

A seminal paper[13] described the used of *o*-alkenylacetophenone for the synthesis of aminonaphthalene: a remarkable one-pot Sonogashira−aminobenzannulation sequence was performed. Both reactions required palladium catalyst and were achieved in the secondary amine as the solvent of the reaction and for up to 3 days. More recently, a new aminobenzannulation method was developed on the basis of the deprotonation of 2-(1-alkynyl)-benzaldimines and a multistep rearrangement cascade.[14]

Our work brings a new contribution for the direct aminobenzannulation reaction. Different amines and conditions have been tested (Table 1) showing that pyrrolidine was the best secondary amine to trigger the cyclization.

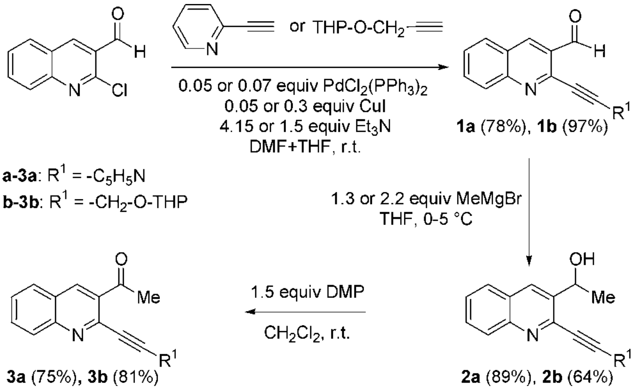
First of all, compounds **3a** and **3b** were easily obtained by three simple and high-yielding steps from commercially available 2-chloro-3-quinoline carboxaldehyde (Scheme 4). Direct Sonogashira[15] reaction on the 2-chloroquinoline position[16] produced **1a** (78%) and **1b** (97%). Grignard addition of MeMgBr, at low temperature, gave the corresponding secondary alcohols **2a** (89%) and **2b** (64%), which were oxidized to the methyl ketones **3a** (75%) and **3b** (81%) with Dess−Martin periodinane (DMP).[17]

Table 1. Aminobenzannulation Conditions

Entry	Starting material	Amine	Product	Method[a] (yield)
1	 **3a**		 **4a**	A (46%) B (78%)[c] C (85%)
2	 **3a**		 **4b**	A (11%) B (50%)[b,c] C (~5%)[b]
3	 **3a**		 **4c**	D (81%)
4	 **3a**		 **4e**	B, C (Quant.)
5	 **3b**		 **4d**	C (84%)

[a] **Method A:** Amine (8 equiv), in hexane, 0−5 °C, $TiCl_4$ (0.7 equiv). After 25 min, starting material was added; the reaction was left for 20 min at 0−5 °C and 25 min at rt and then diluted in dry toluene. Then, $PtCl_2$ (30 mol %) was added, reflux, 17 h. **Method B:** Amine (3 equiv), dry CH_2Cl_2, 4 Å powdered molecular sieves (3 weight equiv), rt for 3−5 h. Then, $PtCl_2$ (15 mol %) added for 17 h, rt. **Method C:** Amine (3 equiv), dry CH_2Cl_2, 4 Å powdered molecular sieves (3 weight equiv), reflux, 3−4 h. **Method D:** Amine (6 equiv), dry CH_2Cl_2, 4 Å powdered molecular sieves (3 weight equiv), Al_2O_3 neutral (1 weight equiv), reflux, 15 h. [b] % conversion calculated by ^1H NMR. [c] Neutral Al_2O_3 (1 weight equiv) was added.

Scheme 4. Synthesis of **3a** and **3b**



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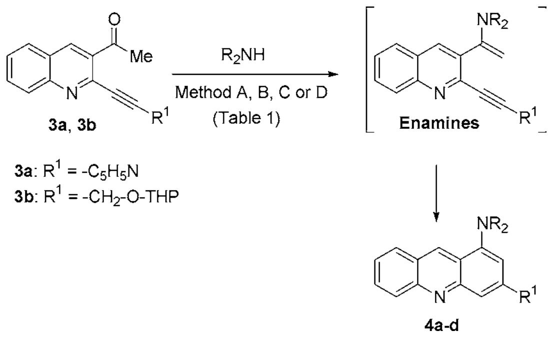
Scheme 5



To form the enamines (Scheme 5), we first used pyrrolidine or piperidine with classical $TiCl_4$ catalysis[18] (Table 1, entries 1 and 2, method A) and tried the cyclization with $PtCl_2$, a catalyst known for promoting enyne cyclization.[19] Interestingly, our enamine-yne substrates did cyclize to the corresponding acridines, but in poor yield (46% for **4a** and 11% for **4b**).

We then decided to adapt an old methodology by using powdered 4 Å molecular sieves with neutral alumina[20] in order to yield the enamine. Thereafter, $PtCl_2$ addition-catalyzed cyclization to the desired acridines occurred in improved yield (entry 1, method B, **4a**, 78%; entry 2, method B, **4b**, 50%).

The reaction was then attempted with only pyrrolidine (3 equiv) and powdered 4 Å molecular sieves in CH_2Cl_2 at reflux. We were delighted to observe a total transformation into the desired cyclized compound **4a** in 85% isolated yield (entry 1, method C). With piperidine, the same methodology gave only traces (~5%) of compound **4b**, the major compound being the enamine intermediate. This difference of reactivity of pyrrolidine versus piperidine has already been well documented in the literature.[21]

Upon comparison with other secondary amines, when morpholine was used Al_2O_3 catalysis was required to form the enamine (entry 3, method D). After cyclization, the 1-morpholino-acridine derivative **4c** was obtained with 81% yield. When diethylamine was used, the reaction stopped at the enamine step: no cyclized product was observed (entry 4, method C) even upon Al_2O_3 and $PtCl_2$ catalysis (entry 4, method B), and only the enamine **4e** was isolated. The aminobenzannulation has already been reported[13] to work with diethylamine; however, the secondary amine was used as the solvent of the reaction, and palladium(II) catalysis was compulsory.

We also tried our new methodology on a different substrate, **3b**, which bears a THP-protected alcohol on the alkyne instead of the former 2-pyridinyl substituent. The aminobenzannulation with pyrrolidine worked out perfectly using method C, and the process yielded **4d** with 84% yield.

In summary, the methodology developed here is efficient and easy to perform since only powdered 4 Å molecular sieves are required for the enamine synthesis step. Also, pyrrolidine has proven to be the best trigger for the aminobenzannulation reaction and without any additional catalyst. We very smoothly obtained new acridine derivatives, even bearing a sensitive protective group. Application of this aminobenzannulation methodology to other heterocyclic structures will be reported in due course.

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

OL050380Z

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