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A novel and simple benzannulation reaction using the potassium salt of methyl mercaptoacetate for the synthesis of 3-aryl-2-methoxycarbonylacridines

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ABSTRACT

A new benzannulation methodology has been developed and applied to the synthesis of 3-aryl-2-methoxycarbonylacridines.

Acridines are classes of fused heterocycles which have been known since the 19th century as pigments and dyes.[1] In the early 1900s their antiseptic activity was studied and during World War I several derivatives of acridine became popular as antibacterial and antimalarial drugs. Nowadays acridines are of considerable interest because of the diverse range of their biological properties, for example, antibacterial[1] and antiparasite.[2] Moreover their anti-cancer properties[3] have also been studied, for instance their inhibitory activity against topoisomerases and telomerase.[4]

A literature survey revealed that acridines are usually constructed via harsh conditions which appear unsuitable for the synthesis of functionalized acridines. For example, high temperatures, and strongly basic or acid media are required for synthesizing acridines via known methods: modification of acridone intermediates,[5] the Bernthsen reaction,[6] cyclization of diphenylamine-2-carboxaldehyde,[7] or by adaptation of the Pfitzinger quinoline synthesis.[8] For the above reasons, the development of a new method to smoothly construct functionalized acridine derivatives is still an important task.

Benzannulation is a useful process in organic synthesis since a wide range of organic molecules contain fused benzene rings. It is a well-known method for the construction of different arenes and benzo-fused heterocycles.[9] For example, benzannulation reactions can be carried out using transition metal carbene complexes[10] and metal-catalyzed[11] or various metal-free methods.[12]

Recently, the Belmont group have developed two new methodologies for the smooth synthesis of acridine nuclei from 2-alkynylquinoline-3-carbaldehydes via benzannulation and aminobenzannulation reactions. The first method requires rhodium, silver- or gold-catalyzed benzannulation of the key quinoline intermediate substituted with a TBS-protected enol–ether and an internal alkyne.[13] The aminobenzannulation process involved Grignard and oxidation reactions of the starting 2-alkynylquinoline-3-carbaldehydes to form the corresponding methyl ketones, followed by addition of amines leading to a smooth cyclization process.[14]

Herein a new, concise synthesis of 3-aryl-2-methoxycarbonylacridines from 2-arylethynylquinoline-3-carbaldehydes via a novel benzannulation reaction is reported. The starting compounds **1a–e** were synthesized by the palladium-catalyzed Sonogashira coupling of commercially available 2-chloroquinoline-3-carbaldehyde with 1-arylacetylenes via literature procedures.[14,15] Treatment of compound **1a** with 1 equiv of the sodium salt of methyl mercaptoacetate in methanol at room temperature led to the formation of a crystalline orange product **2a**. Neither the IR nor ^{13}C NMR spectra of **2a** showed the presence of C≡C or formyl groups in the product. In the ^{1}H NMR spectra, two new aromatic CH singlets at 7.70 and 8.00 ppm along with a singlet due to the methoxy group at 3.94 ppm were observed. These data together with ^{13}C NMR and elemental analysis data indicated that a novel benzannulation reaction had occurred. Thus, it was decided to optimize the conditions to trigger the benzannulation reaction with **1a** and methyl mercaptoacetate as the starting materials (Table 1). The use of potassium methoxide in methanol at room temperature gave the best result (entry 2). While sodium methoxide in methanol provided a slightly lower yield of the desired product **2a**, K_2CO_3 in methanol and dimethylsulfoxide proved to be far less effective (entries 3 and 7). Triethylamine in methanol gave no reaction (en-

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Table 1
Optimization of the reaction conditions for benzannulation

Entry	Solvent	Base	Yield of **2a** (%)
1	CH_3OH	CH_3ONa	79[a]
2	CH_3OH	CH_3OK	90[a]
3	CH_3OH	K_2CO_3	29[a]
4	CH_3OH	Et_3N	0[a,b]
5	C_2H_5OH	C_2H_5OK	21[a]
6	2-C_3H_7OH	2-C_3H_7OK	0[a], 10[b]
7	DMSO	K_2CO_3	38[a]

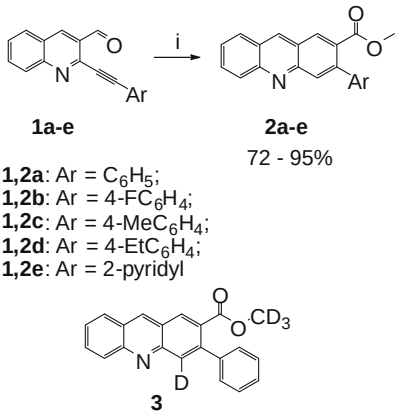
[a] Reactions were performed at rt.
[b] Reaction was performed at reflux temperature.

try 4) while the use of potassium ethoxide or 2-propoxide in appropriate absolute alcohols gave very low yields of **2a** together with undefined mixtures (entries 5 and 6). The reaction of **1a** with methyl mercaptoacetate using potassium deuteriomethoxide in deuterated methanol gave the labelled product **3** (Scheme 1). Thus, the optimal reaction conditions required 1 equiv of potassium methoxide and 1 equiv of methyl mercaptoacetate in methanol at room temperature. Encouraged by these results we decided to perform the reactions of 2-arylethynylquinoline-3-carbaldehydes **1b–e** with methyl mercaptoacetate. The reactions proceeded smoothly to afford good isolated yields of 3-aryl-2-methoxycarbonylacridines **2b–e** (Scheme 1).

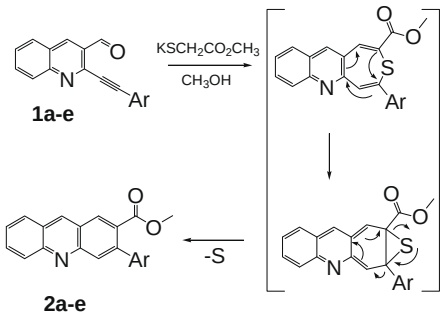
It is assumed, that the benzannulation reaction proceeds via thiepino[4,5-*b*]quinolines, which are formed during nucleophilic attack on the C≡C bond by methyl mercaptoacetate together with a Dieckmann-type condensation of the formyl group with the methylene moiety. It is believed that due to the antiaromatic character of the intermediates, 1,6-electrocyclic ring closure followed by aromatization with elimination of sulfur proceeds very smoothly to form the corresponding 3-aryl-2-methoxycarbonylacridines **2a–e** (Scheme 2). An analogous transformation from benzothiepine to naphthalene derivatives was reported earlier,[16] so our proposed mechanism has good precedent for the final step.

It is noteworthy that methyl mercaptoacetate is the most efficient reagent for this transformation. Other thiols such as 1-butanethiol and benzylthiol did not undergo reaction with the starting compounds to give acridine derivatives.

In summary, a novel, efficient and strightforward procedure for the synthesis of the acridine framework via an unexpected reaction of 2-arylethynylquinoline-3-carbaldehydes with methyl mercaptoacetate has been developed.[17–19] Taking into account that the ester functionality in the molecules can undergo further transformations, this method for the synthesis of the title compounds should be useful for the preparation of various important acridines. Extension of these reactions is currently underway in our laboratory and application of this novel benzannulation methodology to other carbo- or heterocyclic structures will be reported in due course.



Scheme 1. Reagents and conditions: (i) $KSCH_2CO_2CH_3$, CH_3OH, rt, 4 h.



Scheme 2. A proposed mechanism for the benzannulation reaction.

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17. *Typical procedure for the preparation of 3-aryl-2-methoxycarbonylacridines **2a–e***: To a solution of 2-arylethynylquinoline-3-carbaldehyde **1a–e** (0.3 mmol) in methanol (5 mL) a solution of the potassium salt of methyl mercaptoacetate, prepared from potassium (11.7 mg, 0.3 mmol), methyl mercaptoacetate (31.8 mg, 0.3 mmol) and methanol (3 mL) was added. The resulting reaction mixture was stirred for 4 h at room temperature. The solvent was evaporated under reduced pressure, the residue washed with water, filtered and recrystallized from an appropriate solvent to give compounds **2a–e**.
18. *Spectral data of selected 3-aryl-2-methoxycarbonyl acridines. Compound **2a***: Yield 90%, mp 156–157 °C (from MeOH), IR (KBr) ν_{max}/cm^{-1} 1724 (C=O); δ_H (300 MHz, $CDCl_3$): 3.94 (3H, s, OCH_3); 7.37 (1H, t, J = 7.5 Hz, ArH), 7.47–7.58 (3H, m, ArH), 7.70 (1H, s, C(9)-H), 7.72–7.78 (3H, m, ArH), 7.82 (1H, d, J = 8.7 Hz, ArH), 8.00 (1H, s, C(1)-H), 8.12 (1H, d, J = 8.7 Hz, ArH), 8.16 (1H, s, C(4)-H); δ_c (75 MHz, $CDCl_3$): 52.9, 124.5, 126.0, 126.7, 127.3, 127.7, 127.8, 128.0, 128.3, 128.7, 129.6, 129.7, 129.8, 130.2, 130.8, 135.8, 137.4, 149.0, 149.2, 163.7. ($C_{21}H_{15}NO_2$ requires C, 80.49; H, 4.82; N, 4.47. Found: C, 80.54; H, 4.92;

N, 4.41). *Compound* ***3***: Yield 87%, mp 129–130 °C (from 2-PrOH), IR (KBr) ν_{max}/cm^{-1} 1721 (C=O); δ_H (300 MHz, $CDCl_3$): 7.36 (1H, t, *J* = 7.5 Hz, ArH), 7.46–7.57 (3H, m, ArH), 7.69–7.77 (3H, m, ArH), 7.72 (1H, s, C(9)-H), 7.81 (1H, d, *J* = 8.4 Hz, ArH), 7.99 (1H, s, C(1)-H), 8.11 (1H, d, *J* = 8.4 Hz, ArH); δ_c (75 MHz, $CDCl_3$): 53.4 (sept, *J* = 25.1 Hz), 124.5, 125.9, 126.6, 127.3, 127.7 (t, *J* = 26.5 Hz), 127.8, 127.9, 128.3, 128.7, 129.6, 129.8, 130.2, 130.8, 135.7, 137.4, 148.9, 149.1, 163.7. ($C_{21}H_{11}D_4NO_2$ requires C, 79.48; H, D 6.02; N, 4.41. Found: C, 79.52; H, D 5.99; N, 4.44.)

19. Compounds **1b**–**d** and **2b**–**e** were fully characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopic and microanalytical data.