The First and Efficient Synthesis of 7-Aryl-6-methoxycarbonylquinazolines via Unexpected Reaction of 6-Arylethynylpyrimidine-5-carbaldehydes and Methyl Mercaptoacetate

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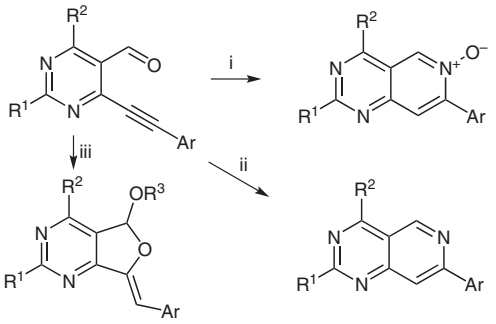
Abstract: A highly concise synthesis of 7-aryl-6-methoxycarbonylquinazolines via reaction of 6-arylethynylpyrimidine-5-carbaldehydes and methyl mercaptoacetate is described.

Key words: quinazolines, benzannulation, alkynes, cyclization

Quinazoline are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties, for example anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive activities.[1] A number of solution- and solid-phase synthesis procedures for the construction of quinazoline heterosystem have recently been advanced. A literature survey revealed that anthranilic acid or anilines with suitable substituents are the most often used starting compound for this purpose.[2] However, to the best of our knowledge, there are only few examples of synthesis of quinazolines from pyrimidine derivatives in the literature[3] and the applicability of these methods is very limited.

Previous works of our group reported that 6-arylethynylpyrimidine-5-carbaldehydes undergo reactions with hydroxylamine, *tert*-butylamine or primary alcohols, therefore we have shown that these compounds are versatile and useful intermediates for the synthesis of pyrido[4,3-*d*]pyrimidine[4] and 5,7-dihydrofuro[3,4-*d*]pyrimidines[5] frameworks (Scheme 1).



Scheme 1 Our previous work. *Reagents and conditions*: (i) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH, reflux; (ii) *t*-$BuNH_2$, 120 °C; (iii) R^3OH, base, reflux.

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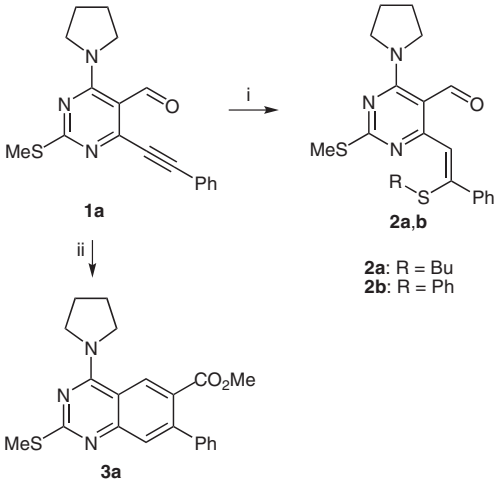
These results logically led us to investigate the reactions of 6-arylethynylpyrimidin-5-carbaldehydes with sulfur nucleophiles. We were pleasantly surprised to find that reaction of the starting compounds with methyl mercaptoacetate led to novel benzannulation reaction. So herein we wish to report on a new, highly concise synthesis of 7-aryl-6-methoxycarbonylquinazolines.

The starting compounds **1** were synthesized by the palladium-catalyzed Sonagashira coupling of the corresponding 2,4-disubstituted 6-chloropyrimidine-5-carbaldehydes with 1-arylacetylenes by the procedure reported earlier by us.[5] Reaction of compound **1a** with an equivalent of sodium butylthiolate or sodium thiophenolate in methanol at room temperature proceeded in expected way and conjugate regio- and stereoselective addition[6] took place and the formation of yellow crystalline products **2a**,**b** was observed (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) RSNa, MeOH, r.t.; (ii) $NaSCH_2CO_2Me$, MeOH, r.t., 2 h.

We were further intrigued to observe the formation of a colorless product, while treatment of compound **1a** with an equivalent of sodium salt of methyl mercaptoacetate in methanol at room temperature. Neither IR spectra nor ^{13}C NMR spectra of **3a** showed the presence of C≡C or formyl groups in molecules. In the ^1H NMR spectra of obtained products two new singlets at δ = 7.45 ppm and δ = 8.64 ppm along with the singlet of methoxy group at δ = 3.62 ppm were observed. These data indicated that not only

conjugate addition of thiolate moiety to the C≡C bond, but also condensation of activated methylene group with formyl functionality had taken place. Thus, the obtained product seemed to be derivative of unknown heterocyclic system, thiepino[4,5-*d*]pyrimidine. However, slow crystallization of **3a** from methanol provided single crystals suitable for the X-ray crystallographic analysis, which enabled the outcome of the reaction to be elucidated unambiguously (Figure 1).[7] We were surprised when crystallographic data of **3a** showed that in reaction of the starting compound with methyl mercaptoacetate a novel benzannulation reaction had taken place and the obtained product was 6-methoxycarbonyl-2-methylthio-7-phenyl-4-pyrrolidinylquinazoline (Figure 1).

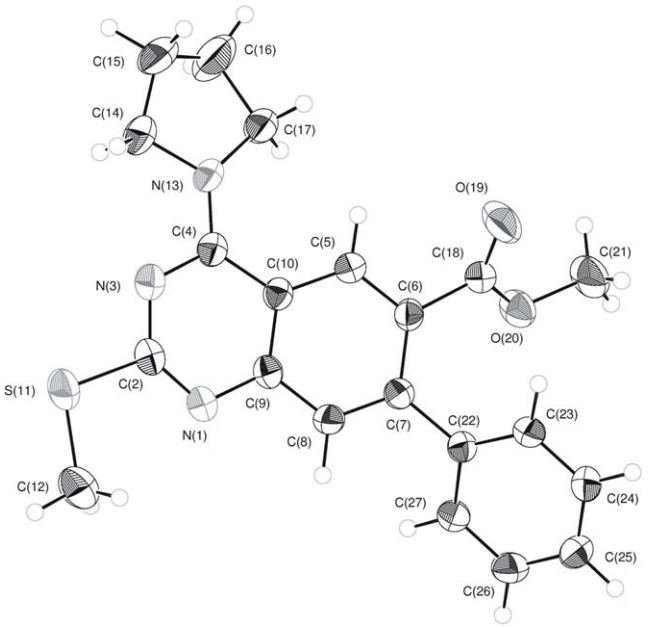


Figure 1 ORTEP drawing of compound **3a**

Thus, we decided to look for the best 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 **3a**, K_2CO_3 in methanol, 2-propanol and dimethylsulfoxide proved to be far less effective (entries 3, 5 and 7). Et_3N in methanol was not successful (entry 4) and use of sodium hydride in absolute THF gave only an undefined mixture (entry 6). So, we found that the optimal reaction conditions were an equivalent of potassium methoxide and an equivalent of methyl mercaptoacetate in methanol at room temperature.

Table 1 Reaction Conditions for Benzannulation

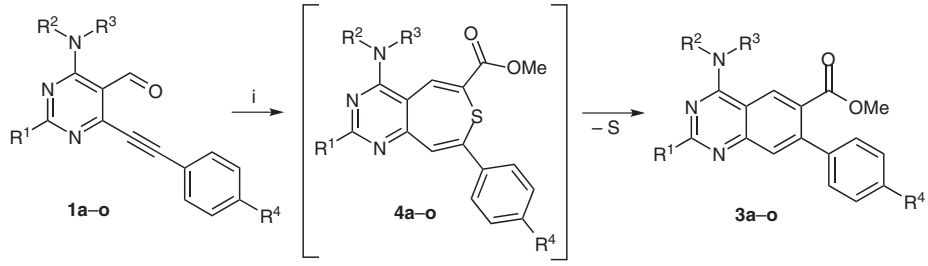
Entry	Solvent	Base	Yield of **3a** (%)
1	MeOH	NaOMe	79[a]
2	MeOH	KOMe	86[a]
3	MeOH	K_2CO_3	42[a]
4	MeOH	Et_3N	0[a,b]
5	*i*-PrOH	K_2CO_3	0,[a] 10[b]
6	THF	NaH	n/a[a,b]
7	DMSO	K_2CO_3	38[a]

[a] Reaction performed at r.t.
[b] Reaction performed at reflux temperature.

Encouraged by these results we decided to perform the reactions of the other 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes **1a–o** with methyl mercaptoacetate (Scheme 3). The results of the synthesis of 7-aryl-6-methoxycarbonylquinazolines **3a–o** by the presented method are summarized in Table 2.

We believe, that the reaction of 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes **1** with methyl mercaptoacetate could proceed via 2,4-disubstituted methyl 8-aryl-6-methoxycarbonylthiepino[4,5-*d*]pyrimidines **4**. We assume, that intermediates **4** due to their unstability undergo smooth 1,6-electrocyclic ring closure and following aromatization with elimination of sulfur to form the corresponding 2,4-disubstituted 7-aryl-6-methoxycarbonylquinazolines **3a–o**. Analogous transformation from benzothiepine to naphthalene derivatives has been reported earlier,[8] so our proposed mechanism seems to be reasonable.

In conclusion, we have developed a novel, simple and high-yielding synthetic method for quinazoline framework via unexpected reaction of 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes with methyl mercaptoacetate. This is the first example for the preparation of the title compounds from 6-arylethynylpyrimidine-5-carbaldehydes and the first example of methyl mercap-



Scheme 3 *Reagents and conditions*: (i) $KSCH_2CO_2Me$, MeOH, r.t., 2 h.

Table 1 Synthesis of 2,4-Disubstituted 7-Aryl-6-methoxycarbonylquinazolines **3a–o**[9,10]

Entry	Starting compound	R^1	NR^2R^3	R^4	Product	Yield (%)
1	**1a**	SMe	$N(CH_2)_4$	H	**3a**	86
2	**1b**	H	NH_2	H	**3b**	90
3	**1c**	H	PhNH	H	**3c**	97
4	**1d**	NH_2	NH_2	H	**3d**	98
5	**1e**	NH_2	$N(CH_2)_4O$	H	**3e**	95
6	**1f**	SMe	NH_2	H	**3f**	90
7	**1g**	SMe	EtNH	H	**3g**	87
8	**1h**	SMe	PhNH	H	**3h**	98
9	**1k**	SMe	PhNH	F	**3k**	95
10	**1l**	SMe	PhNH	Et	**3l**	90
11	**1m**	SMe	$N(CH_2)_4$	Et	**3m**	90
12	**1n**	SMe	$N(CH_2)_4$	F	**3n**	98
13	**1o**	SMe	$N(CH_2)_4O$	H	**3o**	85

toacetate as a trigger for the benzannulation reaction. Taking into account that 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 biologically important quinazolines. Extension of these reactions is currently under way in our laboratory.

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(7) Crystal structure analysis for **3a**: $C_{21}H_{21}N_3O_2S$, M_r = 379.47 g mol^{-1}, monoclinic, space group P21/a, a = 7.5916 (2), b = 19.0791 (4), c = 13.2219 (4) Å, α = 90.00°, β = 94.3120 (9)°, γ = 90.00°, V = 1909.65 (9) Å^3, ρ = 1.320 g/cm^3, F(000) = 800. X-ray diffraction data were collected on a Nonius Kappa CCD diffractometer at 293 K using graphite-monochromated Mo–K_α radiation (λ = 0.71073 Å). Structure **3a** was solved by direct methods with SIR97 program[11] and refined by full-matrix least squares techniques with anisotropic non-hydrogen atoms. Hydrogen atoms were refined in the riding model. The refinement calculations were carried out with the help of SHELX97 program.[12] ORTEP[13] view of the molecule is shown in Figure 1. Crystallographic data for structure **3a** have been deposited at the Cambridge Crystallographic Data Centre (CCDC number 703429).

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(9) **Typical Procedure for the Preparation of 2,4-Disubstituted 7-Aryl-6-methoxycarbonylquinazolines 3a–o**: To a solution of the corresponding 6-arylethynylpyrimidine-5-carbaldehyde **1a–o** (0.3 mmol) in methanol (5 mL) a solution of 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 2 h at r.t. The solvent was evaporated under reduced pressure, the residue was washed with H_2O, filtered and recrystallized to give compounds **3a–o**.
6-Methoxycarbonyl-2-methylthio-7-phenyl-4-pyrrolidinoquinazoline (3a): yield: 86%; mp 185–187 °C (from MeOH). IR (KBr): 1708 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.01 [br s, 4 H, $(CH_2)_2$], 2.54 (s, 3 H, SMe), 3.62 (s, 3 H, OMe), 3.92 [br s, 4 H, $N(CH_2)_2$], 7.37–7.47 (m, 5 H, ArH), 7.45 (s, 1 H, CH), 8.64 (s, 1 H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 13.4, 25.0, 50.6, 51.9, 11.9, 125.0, 127.2, 127.6, 127.9, 128.1, 129.2, 139.7, 144.8, 152.9, 157.5, 167.4, 168.7. Anal. Calcd for $C_{21}H_{21}N_3O_2S$: C, 66.47; H, 5.58; N, 11.07. Found: C, 66.37; H, 5.53; N, 11.11.

(10) Compounds **2a**,**b** and **3b–o** were also fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopic and microanalytical data.

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