Tetrahedron Letters 50 (2009) 6048–6052

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile one-step synthesis of 5-chloro-imidazo[1,5-*a*]quinazoline by microwave irradiation

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ARTICLE INFO

Article history:
Received 4 June 2009
Revised 3 August 2009
Accepted 18 August 2009
Available online 21 August 2009

Keywords:
Imidazoquinazoline
4-Quinazolinone
Microwave

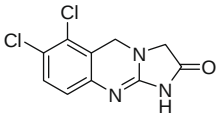
ABSTRACT

A new and facile method has been developed for the one-step synthesis of 5-chloro-imidazo[1,5-*a*]quinazoline by cyclization of *N*-acylanthranilic acid **A** with 2-amino acetamide **B1** or 2-amino-acetonitrile **B2** in the presence of $POCl_3$ under microwave irradiation. 5-chloro-imidazo[1,5-*a*]quinazolines can be further functionalized by displacement of 5-Cl group.

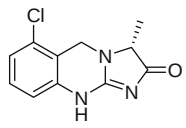
1. Introduction

4-Quinazolinones are of interest to medicinal chemists due to their anticancer, antiviral, antimicrobial, anticonvulsant, and anti-inflammatory activities.[1] Fusing an imidazo moiety with the quinazoline ring affords imidazoquinazolines; two imidazoquinazoline-based drugs, anagrelide and quazinone, are used clinically as anti-thrombotic and cardiotonic agents.[2] Structural variants of imidazoquinazolines can provide new compounds for evaluation against a variety of biological targets. The imidazo[1,5-*a*]quinazolines NNC 14-0185 and NNC 14-0189 have been reported to show promising anticonvulsant profile in rats and mice.[3] In spite of the interesting pharmacological properties of imidazo[1,5-*a*]quinazolines, there are few reports of their synthesis and the known methods require multi-step synthesis from quinazolines.[4]

Anthranilic acid and its derivatives are well-precedented[5] building blocks for the synthesis of quinazolinones. Grimmel reported[6] the synthesis of quinazolinones by heating *N*-acetylanthranilic acids with anilines in the presence of condensing reagents, such as phosphorus trichloride, phosphorus oxychloride, or thionyl chloride. Xue et al. improved[7] the yield for the synthesis of C2, N3-disubstituted-quinazolinones from anilines and *N*-acylanthranilic acids by using acetonitrile as a solvent, but they noted that no 4-quinazolinone was produced in the reactions involving an alkylamine. The present study emerged from optimizing the reaction conditions for the synthesis of quinazolinones from *N*-acylanthranilic acids and 2-amino acetamides: we discovered the formation of a new tricyclic product 5-chloroimidazo[1,5-*a*]quinazoline when $POCl_3$ was used as a condensing reagent. In this Letter, we report the first one-step synthesis of 5-chloroimidazo[1,5-*a*]quinazolines by the cyclization of *N*-acylanthranilic acid with 2-amino acetamides or 2-amino-acetonitriles in the presence of condensing reagent $POCl_3$ and utilizing microwave irradiation.



Anagrelide



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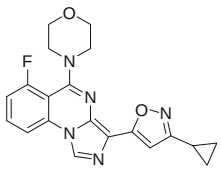
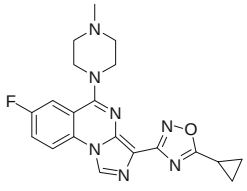


NNC 14-0185



NNC 14-0189

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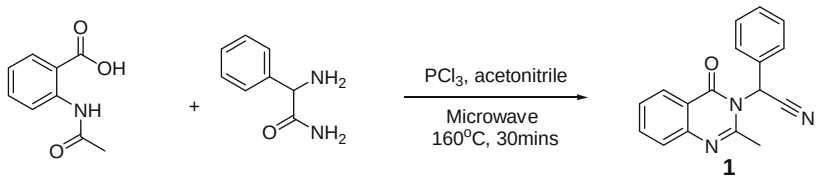
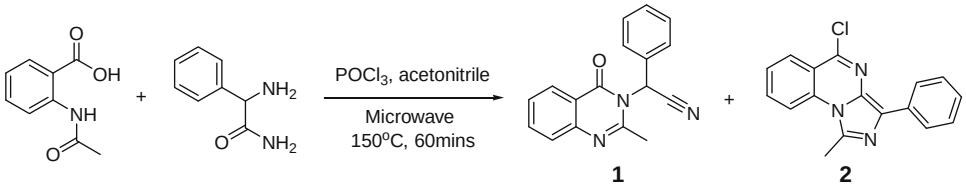
doi:10.1016/j.tetlet.2009.08.054



Scheme 1.



Scheme 2.

2. Results and discussion

Our initial attempts at the formation of imidazo[1,5-*a*]quinazolines were unsuccessful, providing instead the undesired 4-quinazolinone. For example, in the reaction of 2-acetamidobenzoic acid with 2-amino-2-phenylacetamide in the presence of 3 equiv of PCl_3 under microwave irradiation, we observed formation of the 4-quinazolinone with concomitant carboxamide dehydration to afford the 2-acetonitrile-4-quinazolinone **1** as shown in Scheme 1.[8]

Further investigation of this reaction by surveying different condensing reagents, such as PCl_3, $POCl_3$, PCl_5, and $SOCl_2$, indicated that the condensing reagents played a crucial role in determining the product distribution. While $SOCl_2$ gave no cyclized product, PCl_5 provided some quinazolinone but in very poor yield, and PCl_3 afforded exclusively the quinazolinone product **1** in reasonable yield. Interestingly, when $POCl_3$ was used, we obtained a 1:1 mixture of the desired imidazoquinazoline **2** and the quinazolinone **1** (Scheme 2).[9]

The assigned structures for 5-chloro-1-methyl-3-phenylimidazo[1,5-*a*]quinazoline **2** and 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2-phenylacetonitrile **1** were confirmed by single crystal X-ray crystallography (Fig. 1).[10]

Our mechanistic proposal for the formation of the quinazolinone and imidazoquinazoline products is shown in Scheme 3. Both carbonyl groups in 2-acetamidobenzoic acid can be activated by $POCl_3$, the acid is activated as an acid chloride while the acetamide is activated as an acetimidoyl chloride. The formation of the quinazolinone and imidazoquinazoline products can be explained by the amino moiety of 2-amino-2-phenylacetamide attacking two different sites in the activated intermediate of 2-acetamidobenzoic acid: route (a) proceeds via amide formation and carboxamide dehydration to afford a quinzolinone, and route (b) proceeds via amidine formation, carboxamide dehydration, and stepwise cyclization to afford an imidazoquinazoline. During this one-pot cyclization three new bonds were formed.

Utilizing $POCl_3$ as the condensing reagent, we next conducted a substrate survey as shown in Table 1. Varying R_3 on the 2-position of 2-amino acetamide strongly influenced the yield of the imidazoquinazoline product, with a general trend of Me > Ph > H (Table 1, entries 1–3). The introduction of an electron-withdrawing group (R_2) at the 5-position of the 2-acetamidobenzoic acid improved the yield for the formation of the imidazoquinazoline (Table 1, entries 4–9). When R_2 is an electron-donating group, for example, a methoxy group, only a trace amount of the desired imidazoquinazoline was observed in a complex product mixture. In most cases, the main reaction byproduct was the corresponding 2-acetonitrile-4-quinazolinone. The yield ratio of the imidazoquinazoline product to the corresponding quinazolinone of each reaction is shown in Table 1.

Because the carboxamide was dehydrated to a cyano group in the quinazolinone product, we surmised that the nitrile intermediate was formed prior to cyclization. This led us to substitute 2-

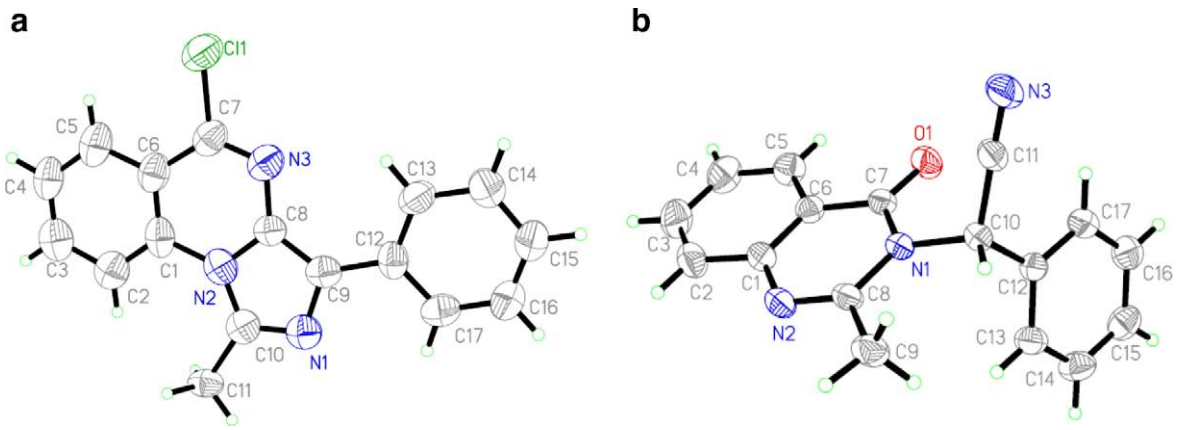
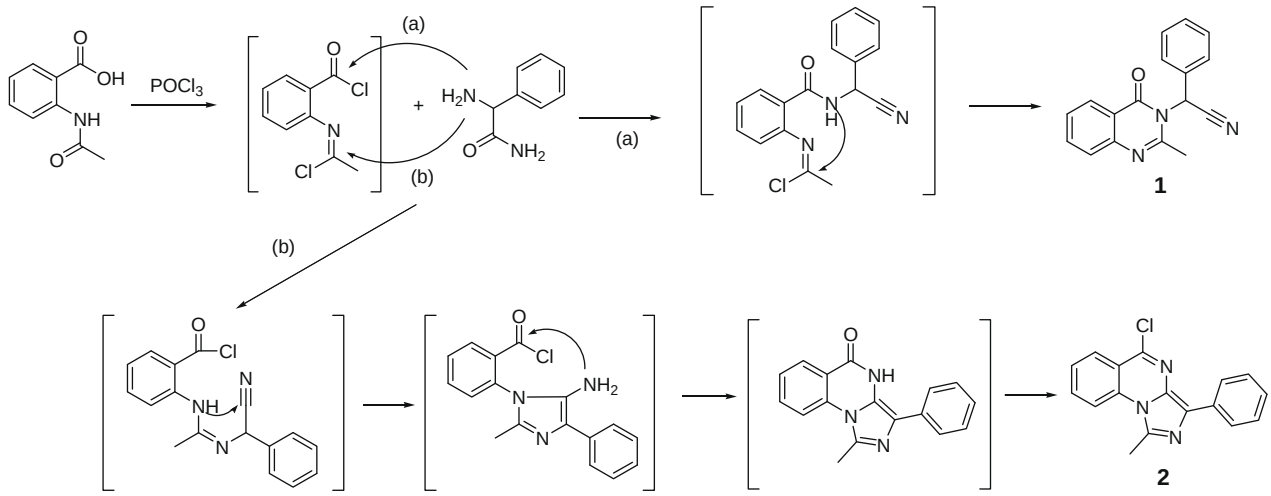
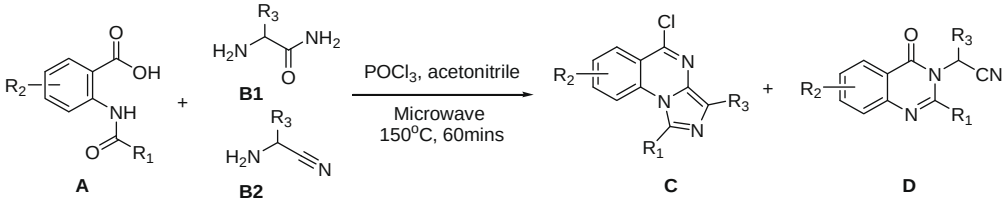


Figure 1. X-ray structure of (a) 5-chloro-1-methyl-3-phenylimidazo[1,5-*a*]quinazoline **2** and (b) 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2-phenylacetonitrile **1**.



Scheme 3.

Table 1
Formation of the imidazoquinazoline under microwave irradiation



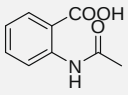
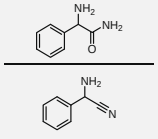
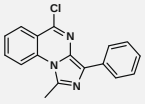
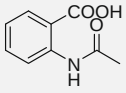
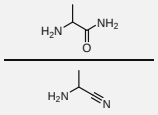
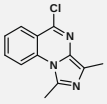
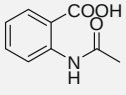
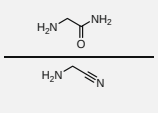
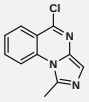
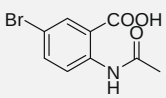
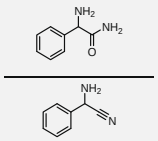
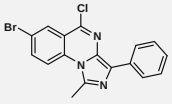
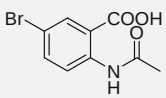
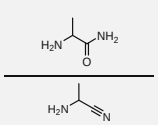
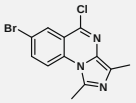
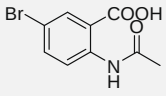
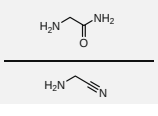
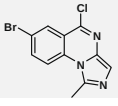
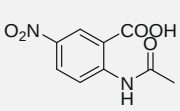
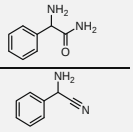
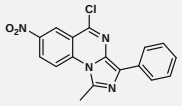
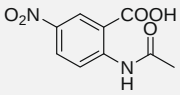
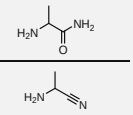
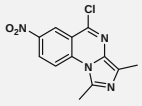
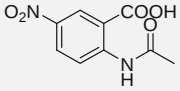
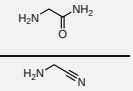
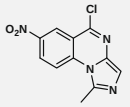
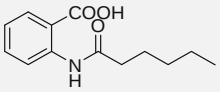
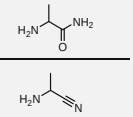
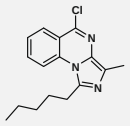
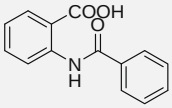
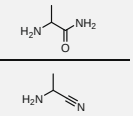
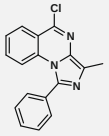
Entry	Substrate A	Substrate B1 / Substrate B2	Product C	Yield of C[a] (%)	Yield ratio C:D
1				30 56	50:50 84:16
2				39 41	68:32 73:27
3				0 21	0:100 31:69
4				36 50	65:35 79:21
5				40 43	73:27 83:17
6				18 26	32:68 42:58

Table 1 (*continued*)

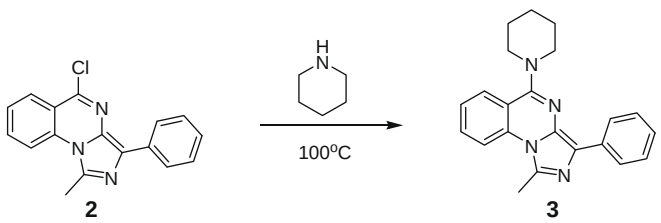
Entry	Substrate A	Substrate B1 / Substrate B2	Product C	Yield of C[a] (%)	Yield ratio C:D
7				45 78	82:18 100:0
8				51 69	86:14 92:8
9				38 46	58:42 68:32
10				25 43	48:52 64:36
11				10 11	63:37 62:38

[a] Yields of the isolated products.

aminoacetonitriles for the corresponding 2-amino acetamides, and we found that 2-aminoacetonitriles improved the yield of the desired imidazoquinazolines. For example, the cyclization of 2-acetamido-5-nitrobenzoic acid with 2-amino-2-phenylacetonitrile afforded exclusively the imidazoquinazoline product in 78% yield (Table 1, entry 7). When 2-aminoacetonitrile was used, the corresponding 5-chloro-imidazoquinazoline was isolated as the major product in nearly every case (exceptions: Table 1, entries 3, 6, and 11) with yields ranging from 41% to 78%. When R_1 is a phenyl group, the yield of the imidazoquinazoline is significantly lower than when R_1 is an alkyl group (Table 1, entry 11).

Finally, it should be noted that the 5-chloro-1-methyl-3-phenylimidazo[1,5-*a*]quinazoline can be further functionalized by displacement of 5-Cl with alkyl amines. For example, the 5-Cl of **2** was displaced by piperidine to afford **3** in 83% yield (Scheme 4).[11]

In conclusion, we have developed a new method for the one-step synthesis of imidazo[1,5-*a*]quinazoline. In this method, the cyclization of *N*-acylanthranilic acid with 2-amino acetamide or 2-amino-acetonitrile in the presence of $POCl_3$ afforded the 5-chloroimidazo[1,5-*a*]quinazolines under microwave irradiation. The yield of imidazoquinazoline was improved by introducing an electron-withdrawing group at the 5-position of 2-acetamidobenzoic acid. This route provided ready access to imidazoquinazolines which can be explored for their pharmacology properties. The structure of the tricyclic imidazoquinazoline was confirmed by X-ray crystal structure analysis.



Scheme 4.

Acknowledgments

The authors thank Dieter Drexler and Joseph Cantone for the HRMS study of all the new compounds.

Supplementary data

Supplementary data (experimental procedures, spectroscopic data for all new compounds, selected ^1H and ^{13}C NMR spectra and X-ray crystallography data for 5-chloro-1-methyl-3-phenylimidazo[1,5-*a*]quinazoline and 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-2-phenyl-acetonitrile) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.054.

References and notes

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8. *Procedure for the Preparation of 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-2-phenylacetonitrile 1 using PCl_3 as condensing reagent*: In a 0.5–2 ml glass

microwave vessel were placed 2-acetamidobenzoic acid (27 mg, 0.15 mmol), 2-amino-2-phenylacetamide (33.8 mg, 0.225 mmol), acetonitrile (1 ml), followed by trichlorophosphine (62 mg, 0.45 mmol). The reaction mixture was heated under microwave irradiation using an *Emrys™ Optimizer* at 160 °C for 30 minutes. The solvent was removed and the residue was purified by PrepHPLC to give the product in 54% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.51 (s, 3H), 7.37–7.48 (m, 5H), 7.52 (t, J = 7.6 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.80 (ddd, J = 8.3, 7.1, 1.4 Hz, 1H), 7.94 (br s, 1H), 8.32 (d, J = 8.3 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 23.9, 45.8, 115.8, 119.6, 125.8, 127.3, 127.5, 127.7, 129.5, 129.7, 131.6, 135.5, 147.0, 152.9, 161.8. HRMS (M+H) calcd for $C_{17}H_{14}N_3O$: 276.1131; found: 276.1127.

9. *Procedure for the preparation of 5-chloro-1-methyl-3-phenyl-imidazo[1,5-a]quinazoline 2 using $POCl_3$ as condensing reagent*: In a 0.5–2 ml glass microwave vessel were placed 2-acetamidobenzoic acid (27 mg, 0.15 mmol), 2-amino-2-phenylacetamide (33.8 mg, 0.225 mmol), acetonitrile (1 ml), followed by phosphoryl trichloride (69 mg, 0.45 mmol). The reaction mixture was heated under microwave irradiation using an *Emrys™ Optimizer* at 150 °C for 60 min. The solvent was removed and the residue was purified by PrepHPLC to give 5-chloro-1-methyl-3-phenyl-imidazo[1,5-*a*]quinazoline **2** in 30% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.06 (s, 3H), 7.29 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.80 (ddd, J = 8.8, 7.3, 1.5 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 8.22 (dd, J = 8.1, 1.5 Hz, 1H), 8.30–8.38 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 19.4, 115.8, 118.3, 126.0, 126.7, 127.2, 128.5, 128.6, 130.0, 131.6, 133.3, 133.7, 135.6, 137.4, 145.2. HRMS (M+H) calcd for $C_{17}H_{13}N_3Cl$: 294.0793; found: 294.0790.
10. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 734596 and 734597.
11. *Procedure for the preparation of 5-piperidinoimidazo[1,5-a]quinazoline 3*: In a 20 ml scintillation vial were placed 5-chloro-1-methyl-3-phenyl-imidazo[1,5-*a*]quinazoline (29 mg, 0.1 mmol) and piperidine (0.5 ml, neat). The reaction mixture was heated at 100 °C. The reaction completed after 1 h as indicated by LCMS. The piperidine was removed and the residue was purified by PrepHPLC to give 5-chloro-1-methyl-3-phenyl-imidazo[1,5-*a*]quinazoline **3** in 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.67–1.96 (6H, m), 3.04 (3H, s), 3.34–3.51 (4H, m), 7.22 (1H, t, J = 7.3 Hz), 7.35–7.52 (3H, m), 7.70 (1H, td, J = 7.9, 1.5 Hz), 7.98 (1H, dd, J = 7.9, 1.3 Hz), 8.10 (1H, d, J = 8.5 Hz), 8.42 (2H, dd, J = 8.3, 1.3 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 19.5, 24.9, 26.0, 51.9, 115.5, 116.1, 124.6, 125.5, 125.7, 125.8, 127.6, 128.4, 131.9, 133.1, 134.8, 135.5, 136.7, 156.3. HRMS (M+H) calcd for $C_{22}H_{22}N_4$: 343.1917; found: 343.1918.