Tetrahedron Letters 52 (2011) 1096–1100

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Facile and efficient generation of quinolone amides from esters using aluminum chloride

Michael K. Schwaebe *, David M. Ryckman, Johnny Y. Nagasawa, Fabrice Pierre, Anne Vialettes, Mustapha Haddach

Cylene Pharmaceuticals, Inc., 5820 Nancy Ridge Dr. Suite 200, San Diego, CA 92121, USA

ARTICLE INFO

Article history:
Received 6 December 2010
Revised 17 December 2010
Accepted 21 December 2010
Available online 7 January 2011

Keywords:
Amide
Ester
Quinolone
Aluminum chloride
Direct conversion
Lewis acid
Acylation

ABSTRACT

Quinolone esters are readily converted into the corresponding amides using aluminum chloride at room temperature in excellent yields and purities. The method is both general and scalable to multi-kilogram quantities.

Quinolones have a long and rich history as chemotherapeutic antibacterial agents that eradicate bacteria by interfering with DNA replication, transcription, and repair.[1] Their broad spectrum activity results from the inhibition of bacterial DNA gyrase and topoisomerase IV.[2] Certain sub-classes of quinolones have also been reported to be active against cancer cells by means of inhibiting human Topoisomerases I and II.[3] We have recently discovered a new class of quinolones for the treatment of cancer, which act through a novel mechanism of inhibition of the DNA Polymerase I complex (Pol I).[4] By replacing the carboxylic acid moiety with amides in certain quinolones we have achieved selective Pol I inhibition, allowing the discovery of several promising drug candidates for oncology. In the course of our work, we encountered some challenging amide syntheses when utilizing classical reaction conditions. We, therefore, sought to develop a more versatile and practical synthesis of quinolone amides, reported herein.

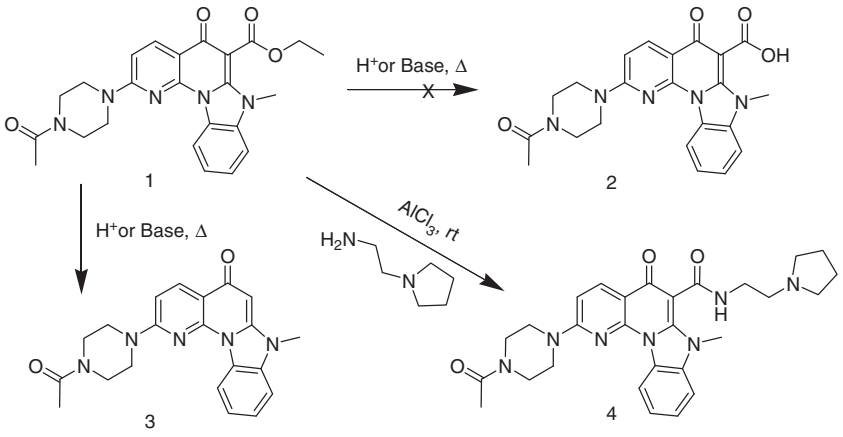
One substrate that could not be treated under classical conditions was the naphthyridine benzimidazole ester **1** (Scheme 1).[5] For closely related scaffolds we typically converted the ester into acid **2** which could be subsequently treated with coupling agents to afford the desired amide. However, hydrolysis of ester **1** under both basic and acidic conditions led to decarboxylation, affording compound **3**. Under thermal conditions, the decarboxylation was also the prominent reaction. Without an efficient means to generate the carboxylic acid **2** in the desired quantities, we sought to craft an alternate method to form the amide bond via a direct conversion of ester **1** into amide **4** at an ambient temperature (Scheme 1).

We examined a variety of conditions to directly affect the transformation. Because the ester exhibits thermal instability any successful reaction would require performance at or below room temperature. While many mild Lewis acids proved ineffective, aluminum chloride emerged as an encouraging coupling reagent (Scheme 1).[6] With 1.5 equiv of both amine and aluminum chloride in dichloromethane (DCM) at room temperature, the reaction stalled at approximately 50% conversion and, therefore, yielded only 15% of the corresponding amide **4.**

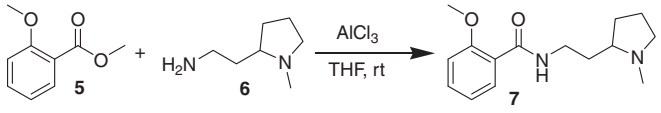
In an effort to identify the optimal stoichiometry for completion of the reaction, we performed the transformation with a model substrate, methyl-2-methoxy benzoate **5** (Scheme 2). We envisioned that ester **5** might be activated by chelation of aluminum with the ester and the methoxy groups, mimicking the dicarbonyl moiety present in quinolone esters. Another advantage of using **5** resulted from the low molecular weight of amide **7**, allowing quick GC–MS monitoring of the reaction. The modeled reactions were performed at room temperature in THF on a 1 mM scale by adding aluminum chloride as a 0.5 M solution in THF. Both amine **6** and aluminum chloride were arrayed from

* Corresponding author. Tel.: +1 858 875 5112; fax: +1 858 875 5101.
E-mail address: mschwaebe@cylenepharma.com (M.K. Schwaebe).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.12.108



Scheme 1. Hydrolysis of quinolone ester **1**.



Scheme 2. Methyl-2-methoxybenzoate as a model reagent for quinolone amide synthesis.

1.0 to 3.0 equiv in 0.5 equiv increments with monitoring at 4, 8, and 24 h.

As illustrated in Table 1, after 24 h at room temperature all reactions using more than 1.5 equiv of the amine and aluminum chloride went to completion. Additionally, the reaction could be further accelerated using excess equivalents of the reagents such that the reaction could be completed in a matter of a few hours. However, it was important to maintain the balance of amine and aluminum to avoid a dramatic decrease of the yield of amide **7** (Table 1).

Application of the optimized conditions to a variety of quinolone scaffolds and amines (Tables 2 and 3) revealed that the reaction was remarkably versatile, scalable, and capable of tolerating a wide range of functionalities. The reaction was selective for primary amines over secondary amines (example 7) with none of the tertiary amide detected in the product. Benzyl amines (example 14) as well as anilines (example 5) and hydrazines (example 13) were also efficient coupling partners. Acid labile protecting groups, such as the Boc group, also tolerated the reaction conditions (example 11).

Moreover, we determined that the reaction could be successfully executed in a library format by the addition of aluminum chloride as a dilute solution in THF. Under those conditions, we have been able to prepare more than 2500 different amide analogs. Additionally, the reaction performed well on a kilogram scale. The exothermic nature of the reaction could be easily controlled either by the rate of addition of the amine or by adding the aluminum chloride in small portions. Due to the strong chelating effect of the aluminum with the dicarbonyl group the workup utilizes either a basic aqueous Rochelle's Salt solution or a treatment with a 50% sodium hydroxide solution and filtration of the resultant aluminum hydroxide.

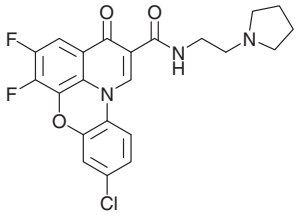
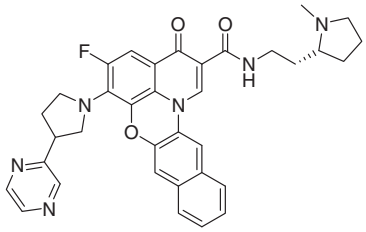
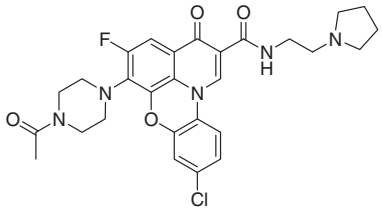
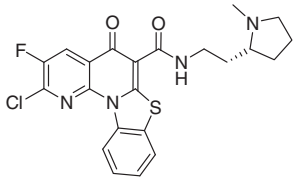
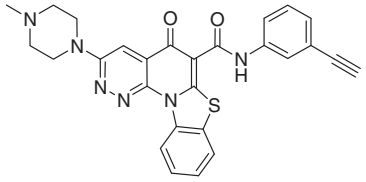
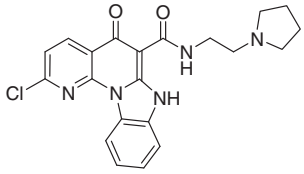
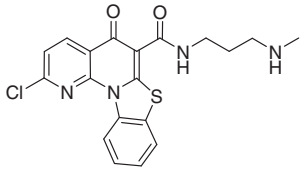
While many of the substrates examined readily underwent transformation, certain cases presented additional challenges (Table 3). Reactions involving hindered and secondary amines or which utilized scaffolds that contained basic nitrogen (such as in examples 8 and 9) required an additional amount of base (Et_3N, DBU, or excess of coupling amine). For basic starting quinolones, the additional amount of base was used to prevent the scaffold/aluminum complex from precipitating out of the reaction mixture. Indeed, in a separate experiment, the ester shown in example 8 when treated with 1.0 equiv of aluminum chloride in DCM precipitated out of the solution as a complex salt. The addition of 1 equiv of base (Et_3N, DBU or 1-(2-aminoethyl)pyrrolidine) induced dissolution of the complex and subsequent reaction with 1-(2-aminoethyl)pyrrolidine to yield the desired amide product. In many instances, a confluence of factors, such as a strongly basic scaffold and a weakly basic coupling amine mandated that an even greater excess of base be used. In example 8 where 6 equiv of the coupling basic amine was used, the reaction proceeded to completion and the amide was isolated in 92% yield. On the contrary, in example 11 where only 1.5 equiv of amine was used without extra base, the reaction stalled at 70% conversion.

In the case of example 8, the reaction required 2 equiv of aluminum chloride, 2 equiv of the desired amine, and 4 equiv of DBU. Alternately, we achieved the transformation with 6 equiv of the desired amine. The reaction proceeded at 0 °C in DCM and was complete in 2 h, resulting in a 92% yield of the product on a 200 g scale.[7] The workup involved quenching the reaction with a tartaric acid solution, discarding the organic layer then adjusting the pH >13 with a 10% sodium hydroxide solution and extraction by DCM.

Table 1
Influence of reagent stoichiometry and time on conversion of **5** to **7**

	Aluminum chloride equivalents				
Amine equivalents	1	1.5	2	2.5	3
	% Conversion at 4 h				
1	37	35	25	10	6
1.5	44	50	71	53	48
2	41	56	78	89	79
2.5	4	47	77	92	89
3	2	54	80	89	100
	% Conversion at 8 h				
1	34	32	28	13	13
1.5	58	62	82	65	60
2	67	63	95	95	92
2.5	10	72	95	100	98
3	2	75	92	99	100
	% Conversion at 24 h				
1	48	46	31	14	7
1.5	73	68	89	74	60
2	80	77	100	100	100
2.5	68	85	100	100	100
3	13	91	100	100	100

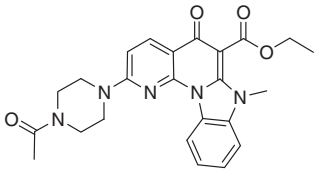
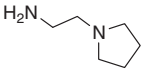
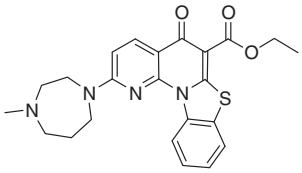
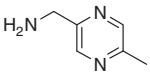
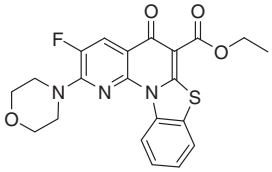
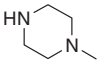
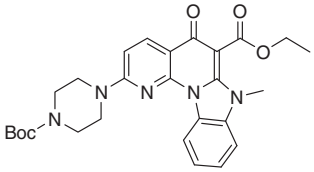
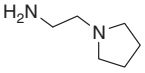
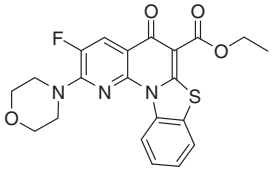
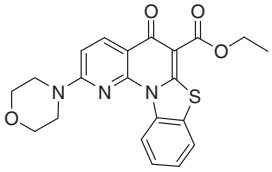
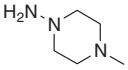
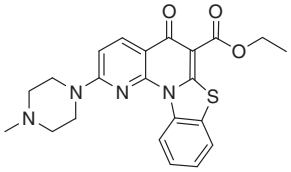
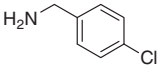
Table 2
Reaction scale and yields of quinolone amides using 1.5 equiv each of the amine and aluminum chloride[a]

Ex.	Amide product[a]	Scale (g)	Isolated yield (%)
1		2.0	99
2[b]		458	98.5
3		5.9	74
4		0.99	74
5[c]		0.06	60
6		1.0	67
7		2.0	86

[a] 1.5 equiv each of the amine and aluminum chloride unless otherwise noted.
[b] 1.2 equiv of the amine and 1.0 equiv of aluminum chloride.
[c] 2.0 equiv of each of the amine and aluminum chloride.

Thus we have demonstrated the utility of aluminum chloride as a useful activating agent for the direct conversion of quinolone esters to their corresponding amides. In many cases the reaction afforded products otherwise not obtainable through traditional amide bond formation from their corresponding carboxylic acids. Due to its increased air handling stability over trialkylaluminum reagents, aluminum chloride is our reagent of choice that could be used even on a kilogram scale. Although this is clearly not an entirely novel synthetic approach to making amides, we feel that the scope of possibilities for this approach of general amide synthesis is greatly underrepresented in the literature.

Table 3
Amide reactions with aluminum chloride requiring additional base

Ex.	Ester	Scale (g)	Amine	Equiv DBU	Equiv amine	Equiv $AlCl_3$	Isolated yield (%)
8		200		0	6.0	2.0	92
9		139.1		3.0	1.8	1.2	87
10		2.05		2.1	1.5	1.5	82
11		0.50		0	1.5	1.5	70
12		0.30		5.5	3.0	3.0	65
13		0.10		3.0	2.0	2.0	70
14		0.03		4.0	2.0	2.0	61

Acknowledgements

The authors are grateful to Dr. George Yiannikouros for his insight into the utilization of aluminum chloride for the direct amidation of quinolone esters.

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7. To a slurry of the ester **8** (200 g, 0.447 mol) and 1-(2-aminoethyl)-pyrrolidine (306 g, 2.68 mol, 6.0 equiv) in methylene chloride (2.2 L) was added aluminum chloride (90 g, 0.675 mol) at 0 °C portion-wise over 30 min maintaining the temperature <15 °C. The mixture was stirred at 0 °C for 2 h then allowed to

come to room temperature overnight. The reaction was cooled with the aid of an ice bath and a saturated solution of L-tartaric acid was added (1.5 L). The mixture was allowed to stir until hydrolysis was complete. The organic layer was removed and the aqueous layer was washed with DCM (500 mL). The aqueous layer was then chilled in an ice bath and basified to pH >13 with a 1 N solution of NaOH. A 9:1 mixture of DCM/methanol was added (200 mL) followed by solid sodium chloride (3 kg). The aqueous layer was then separated from the organic layer and extracted with the DCM/methanol mixture (200 mL × 4). The combined extracts were dried over sodium sulfate (300 g) and the solvent was removed in vacuo. The residual solids were co-evaporated with acetonitrile (3 × 200 mL). Acetonitrile was added (4.0 L) and the slurry was stirred at 40 °C for 30 min then filtered and dried in a vacuum oven to afford the amide as a pale off-white solid (212 g, 411.4 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (1H, t, J = 5.6 Hz), 8.82 (1H, d, J = 7.6 Hz), 8.56 (1H, d, J = 8.4 Hz), 7.41 (3H, m), 8.83 (1H, d, J = 9.2 Hz), 3.89 (4H, br m), 3.82 (2H, br m), 3.81 (3H, s), 3.75 (2H, br m), 3.65 (2H, q, J = 7.2 Hz), 2.78 (2H, t, J = 7.2 Hz), 2.63 (4H, br t), 2.21 (3H, s), 1.81 (4H, br m); LC–MS (287 nm): R_t = 11.90 min (98.9%); EIMS (pos) m/z 516.5 $[M+H]^+$.