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4-Quinolone fused heterocyclic ring systems by intramolecular reactions of 4-quinolone-2-carboxamides

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Dedicated to Professor Lucio Merlini on the occasion of his 80th birthday

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ABSTRACT

A versatile synthetic route to new 4-quinolone-based polycyclic systems is described. TFA-catalyzed intramolecular reaction of N-unsubstituted quinolone-2-carboxylic acid amides gives structurally diverse compounds, depending on the length of the chain. Acid treatment of β-oxoamides furnishes 3H-pyrazino[1,2-a]quinoline-4,6-diones, due to the nucleophilic attack of N-1 to the carbonyl group, whereas TFA treatment of δ- and ε-oxoamides leads to the formation of tetracyclic compounds by a tandem heteroannulation reaction.

1. Introduction

The quinolone moiety is an important structural unit in medicinal chemistry and many compounds with this scaffold have shown a broad range of biological properties including anticancer,[1] antimicrobial,[2] antiviral[3] and antimalarial[4] activity.

In pursuance of our research on the development of new antitumor compounds, we became interested in accessing structurally diverse heterocyclic rings containing the quinolone moiety.

In recent papers[5] we reported that the TFA-catalyzed intramolecular Friedel–Crafts cyclization of indole-2-carboxylic acid β- or γ-oxoamides (**1**) represented a simple synthesis of β-carbolin-1-ones (**2**, *m*=0) or dihydro-2H-azepino[3,4-b]indol-1-ones (**2**, *m*=1) (Scheme 1). Conversely, acid treatment of δ-, ε-, and ζ-oxoamides preferentially gave intermediate *N*-acyliminium ions, which cyclized into the novel heterocyclic rings pyrrolizino[2,1-b]indole (**4**, *m*=1), indolizino[2,1-b]indole (**4**, *m*=2), and 9a,11-diaza-indeno[1,2-a]azulene (**4**, *m*=3).[6]

As the method could provide a route to novel heterocyclic systems, we thought to extend the study to the preparation of quinolone-fused rings.

Although numerous efforts have been made to modify quinolones, there are currently few reports concerning electrophilic substitutions at C-3 of 4-quinolone rings, even though 4-quinolone is known to be in tautomeric equilibrium with its phenol form.[7] A survey of literature revealed few examples of Friedel–Crafts alkylation[8] and acylation of 4-quinolones.[9] Chlorination,[10] bromination[11] and iodination[12] reactions of 4-oxo-1,4-dihydro-quinoline-2-carboxylic acid derivatives are reported as well.

These findings motivated us to apply the synthetic sequence to 4-quinolone-2-carboxamides. We herein describe the outcome of these reactions.

2. Results and discussion

The investigation began with *N*-methyl kynurenic acid **5a**,[13] which was obtained by treatment of *N*-methylaniline with DMAD, followed by cyclization with PPA and basic hydrolysis.[14]

The coupling of **5a** with 2-aminoethanol, through WSC and HOBt, gave the alcohol **6a**. Oxidation of **6a**, followed by treatment with TFA afforded the expected tricyclic compound **8**, although in poor yield (21% overall) (Scheme 2). The yield was increased by coupling **5a** with commercially available aminoacetaldehyde diethylacetal to obtain the amide **7a** in 88% yield. Treatment of **7a**

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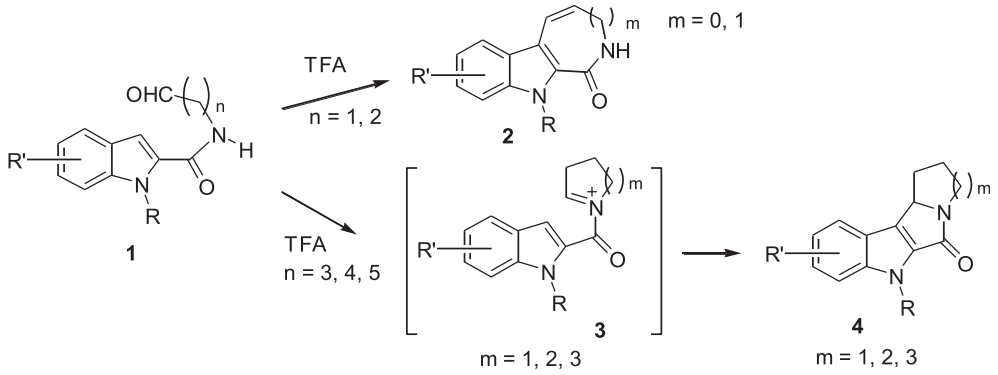
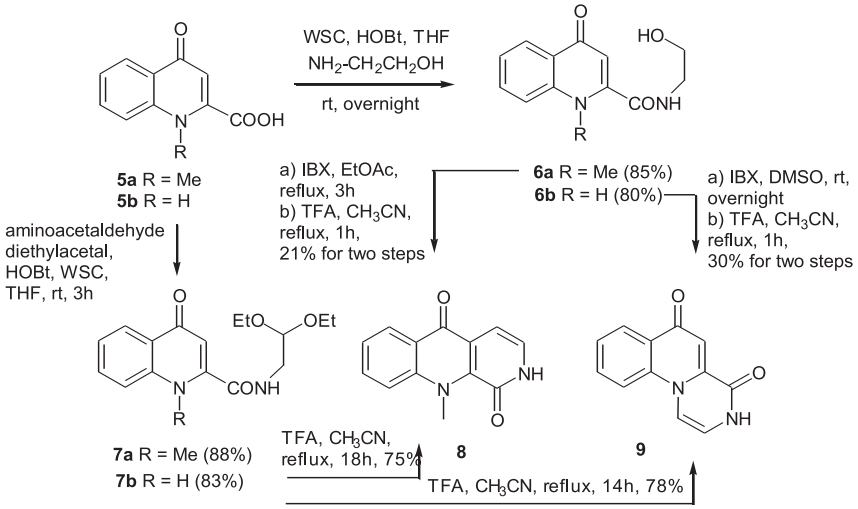


Scheme 1. TFA-catalyzed intramolecular Friedel–Crafts cyclization of indole-2-carboxylic acid oxoamides.



Scheme 2. Synthesis of 10-methyl-2,10-dihydrobenzo[b][1,7]naphthyridine-1,5-dione and 3H-pyrazino[1,2-a]quinoline-4,6-dione.

with TFA gave the cyclization product in 75% yield. When the sequence was performed on the free-NH quinolone **5b**, the reaction proceeded smoothly to give compound **9**, derived from the attack of N-1 to the carbonyl group of the intermediate aldehyde, followed by elimination. Compound **9** was also obtained from the intermediate acetal **7b**, whereas the product of cyclization at C-3 was not isolated at all. There are currently no reports on the synthesis of 2,10-dihydro-benzo[b][1,7]naphthyridine-1,5-diones (**8**) or 3H-pyrazino[1,2-a]quinoline-4,6-diones (**9**). Riepl et al. reported the preparation of 5,7-dihydrodibenzo[b,f][1,7]naphthyridine-6,12-diones by a Fischer type rearrangement reaction.[15] However, the versatility of this methodology was strongly limited by the need to use freshly prepared symmetric 1,2-diarylhydrazines.

To evaluate the influence of the chain length on the cyclization, the reactivity of δ- and ε-oxamides was investigated as well.

When the coupling reaction of *N*-methyl kynurenic acid **5a** was carried out with 4-aminobutanol, alcohol **10a** was obtained (Scheme 3). Oxidation of **10a**, followed by treatment with TFA, gave the enamide **11a**. The same result was obtained when the quinolone nitrogen was protected with a benzyl group (compound **11b**).

This confirmed that the carbonyl group underwent a nucleophilic attack by the amide nitrogen. However, unlike the case of indole,[6] the lower reactivity of the quinolone ring towards the electrophilic substitution prevented the acid-catalyzed intramolecular cyclization and gave rise to compounds **11a**–**b** by an elimination reaction.

Interestingly, oxidation followed by acid treatment of compounds **12a**–**b**, obtained from kynurenic acid **5b**, gave the new compounds **13a**–**b** (Scheme 3). In this case, a tandem heteroannulation reaction – which is most likely due to a first nucleophilic attack of the amide nitrogen to the aldehyde, followed by the N-1 attack on the pentaatomic intermediate ring – furnishes a tetracyclic fused system.

As compound **13a** showed antitumor activity (IC_{50}=10 μM) on H460 tumor cell lines,[16] the scope of the reaction was explored by preparing differently substituted analogues.

Accordingly, treatment of kynurenic acid **5b** with 2-(2-aminophenyl)ethanol gave the alcohol **14**, which was oxidized to the corresponding aldehyde, in its turn converted into the pentacyclic derivative **15** by the usual treatment with TFA (Scheme 3).

Compounds **21a**–**d**, bearing substituents on ring A were obtained from the suitable anilines **16a**–**b** (Scheme 4). Further elaboration of the bromoderivative **21b** via Suzuki-Miyaura palladium-catalyzed cross-coupling reactions generated compounds **21c** and **21d**.

3. Conclusions

In conclusion, we have devised a reliable synthetic route to 4-quinolone-based fused systems starting from 4-quinolone-2-carboxylic acid oxoamides. The acid-catalyzed intramolecular reaction of N-unsubstituted quinolones gives structurally diverse