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Synthesis of 4-hydroxyquinoline-2,3-dicarboxylates using *N*-(2-aminobenzoyl)benzotriazoles

İlhami Çelik*, Fatoş Yıldız

Department of Chemistry, Faculty of Science, Anadolu University, 26470, Eskişehir, Turkey

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ABSTRACT

A method for the preparation of 4-hydroxyquinoline-2,3-dicarboxylates has been developed by aza-Michael addition reaction of *N*-(2-aminobenzoyl)benzotriazoles with dimethyl acetylenedicarboxylate. 4-Hydroxyquinoline-2,3-dicarboxylates were obtained in moderate to good yields (53–87%).

1. Introduction

4-Quinolones comprise an important class of synthetic antibiotics used in the treatment of various infectious diseases, including respiratory tract, urinary tract, gastrointestinal and skin infections, and sexually transmitted diseases.[1–3] There are other works documenting their use for the treatment of cancer[4] and AIDS[5] besides their antibacterial activity.

The synthetic antibiotics containing 4-quinolone ring such as Norfloxacin, Sparfloxacin, and Moxifloxacin (Fig. 1) bear the carboxylic acid moiety at the 3-position. The decarboxylation of 4-hydroxyquinoline-2,3-dicarboxylate derivatives provide potential access to other analogues. Additionally, pyridazino-quinoline-triones and 4-aminoquinoline-2,3-dicarboxylates obtained by using 4-hydroxyquinoline-2,3-dicarboxylates have been found to have a potent activity in the treatment of neuropathic pain,[6] Shigellosis, a bacterial disease[7] and used as beta-secretase inhibitors in the treatment of Alzheimer's disease.[8]

4-Hydroxyquinoline-2,3-dicarboxylates were prepared by using various methods including (i) the reaction of aromatic *o*-amino esters with dialkyl acetylenedicarboxylates in presence of base catalyst[9]; (ii) *N*-methylisatoic anhydride with alkyl 2-oxobutanedioate having active methylene group[10]; (iii) pyrolysis of 4,5-dimethoxycarbonyl-1-aryl-1H-pyrrole-2,3-dion[11]; (iv) thermal rearrangement of diazo compounds obtained from the reaction of phenylazide with olefins substituted by electron-withdrawing groups at the high temperature[12] (Scheme 1). These literature methods suffer from some disadvantages such as low yields, harsh reaction conditions, toxic reagents and difficulties to prepare the starting materials.

Being a different application of *N*-acylbenzotriazoles, *N*-(2-aminobenzoyl)benzotriazoles are stable reagents that have been utilized as important synthons for the synthesis of anthranilic acid amides,[13] esters and thioesters[14] as well as heterocycles.[15] *N*-(2-Aminobenzoyl)benzotriazoles are easily prepared in crystalline form and are stable to moisture. Herein, we report a novel synthesis of 4-hydroxyquinoline-2,3-dicarboxylates via aza-Michael addition reaction of *N*-(2-aminobenzoyl)benzotriazoles with dimethyl acetylenedicarboxylate under catalyst-free conditions.

2. Results and discussion

To obtain 4-hydroxyquinoline-2,3-dicarboxylate **3a**, we initially tried the reaction of *N*-(2-aminobenzoyl) benzotriazole **1a** with 2-oxobutanedioate **2** in the presence of *t*-BuOK and different solvents (Table 1). However, we could not obtain 4-hydroxyquinoline-2,3-dicarboxylates in good yields. Then, we changed our plan to obtain 4-hydroxyquinoline-2,3-dicarboxylates **3a**. We first tried the

* Corresponding author.
E-mail address: ilcelik@anadolu.edu.tr (İ. Çelik).

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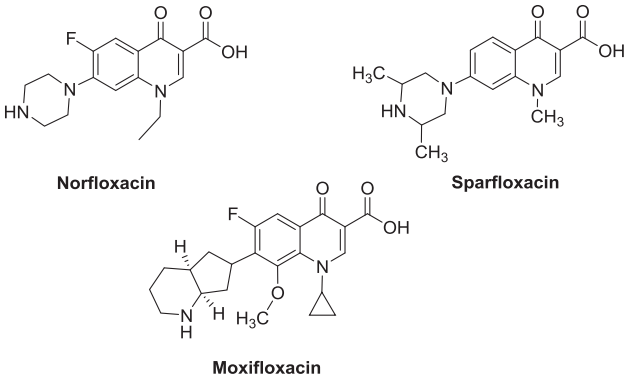
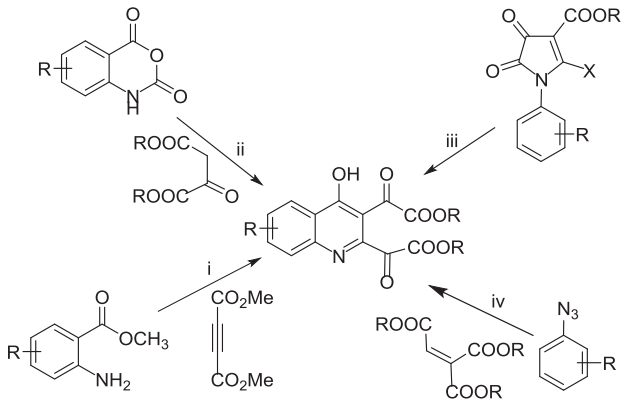
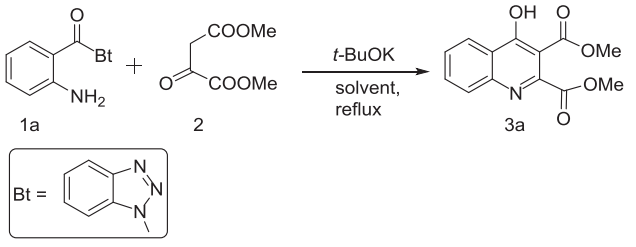


Fig. 1. Structure of some synthetic antibiotics containing 4-quinolone ring.



Scheme 1. Literature methods for the synthesis of 4-hydroxyquinoline-2,3-dicarboxylates.

Table 1
Reaction of *N*-(2-aminobenzoyl)benzotriazole with 2-oxobutanedioat in the different conditions.



Entry	Solvent	Base	Time (h)	Product	Yield (%)
1	THF	*t*-BuOK	12 (rt)	**3a**	–
2	THF	*t*-BuOK	48 (reflux)	**3a**	6
3	*t*-BuOH	*t*-BuOK	12 (rt)	**3a**	–
4	*t*-BuOH	*t*-BuOK	48 (reflux)	**3a**	21
5	DMF	*t*-BuOK	12 (rt)/48 (reflux)	**3a**	–
6	Diphenylether	*t*-BuOK	12 (rt)/48 (reflux)	**3a**	–
7	Dioxane	*t*-BuOK	48 (reflux)	**3a**	24

reaction of *N*-(2-aminobenzoyl) benzotriazole **1a** with dimethyl acetylenedicarboxylate **4** in the presence of *t*-BuOK and then in the absent of base catalyst. 4-Hydroxyquinoline-2,3-dicarboxylates **3a** were obtained in 67% yield when the reaction was performed in the presence of *t*-BuOK. It was found that the yield increased from 68% to 85% when the reaction was performed in the absent of base catalyst (Table 2).

With the optimized reaction conditions in hand, we then turned our attention to explore the generality of this reaction for the preparation of 4-hydroxyquinoline-2,3-dicarboxylates bearing different substituents (Scheme 2). The substituted 4-hydroxyquinoline-2,3-dicarboxylates (**3a**-**3m**) were successfully synthesized in moderate to good yields, except **3i** (Scheme 2). The reason for not observing **3i** might be due to the electron withdrawing effect of two bromides in the aromatic ring.

The structures of obtained compounds were identified by NMR spectroscopy and HRMS spectrometry. During ^{1}H NMR analysis for **3a** in $CDCl_3$, we observed that there was a mixture containing two tautomeric forms. To assign enolic OH and NH proton, we performed ^{1}H-^{15}N HSQC experiment for **3a** (Fig. 2). The characteristic singlet observed around 12.50 ppm in the ^{1}H-^{15}N HSQC spectra was assigned to enolic OH proton due to not observing the cross peak between H and N. A characteristic singlet observed around 9.18 ppm in the ^{1}H-^{15}N HSQC spectra was assigned to NH proton due to the cross peak between H and N although references[10–12] reported that a singlet observed around 12.50 ppm in the ^{1}H NMR spectra were assigned the NH proton. It was thought that these tautomeric forms were 4-hydroxyquinoline and 4-quinolone forms. The tautomerization rate of 4-hydroxyquinoline and 4-quinolone forms is 72% and 28% respectively.

A possible mechanism according to the formation of annulation product is proposed in Scheme 3. The reaction would be initiated by aza-Michael addition of *N*-(2-aminobenzoyl) benzotriazole to dimethyl acetylenedicarboxylate. Then, the subsequent cyclization of formed intermediate **A** affords intermediate **B** and benzotriazolyl anion. The addition of benzotriazolyl anion to dimethyl acetylenedicarboxylate gives intermediate **C**. In the last step, the final product **3a** and by-product **5** are obtained with deprotonation of intermediate **B**.

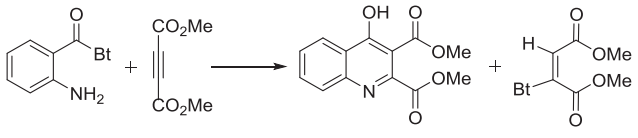
3. Conclusions

In conclusion, a novel and simple annulation reaction of *N*-(2-aminobenzoyl)benzotriazoles with dimethyl acetylenedicarboxylate has been developed. This method provides easily accessible starting compounds, a general and straightforward way to prepare 4-hydroxyquinoline-2,3-dicarboxylates in the absent of catalyst and tolerates a wide range of functional groups. Further investigation for *N*-(2-aminobenzoyl) benzotriazole-mediated synthesis of other heterocyclic and carbocyclic systems induced annulation reaction is ongoing in our laboratory.

4. Experimental section

All chemicals were purchased from commercial suppliers and used without further purification. *N*-(2-aminobenzoyl)

Table 2
Reaction of *N*-(2-Aminobenzoyl)benzotriazole with dimethyl acetylenedicarboxylate in the different Conditions.



Entry	Solvent	Base	Time (h)	Product	Yield (%)
1	*t*-BuOH	*t*-BuOK	12 (reflux)	**3a**	67
2	*t*-BuOH	–	12 (reflux)	**3a**	85