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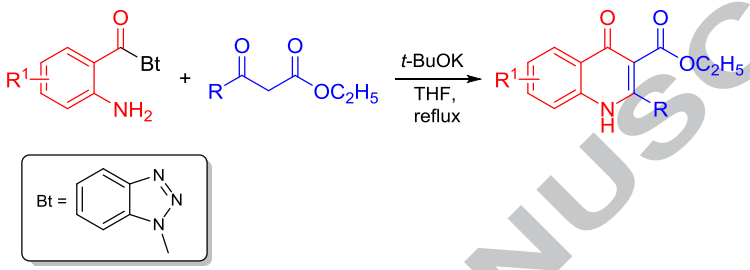

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N-(2-aminobenzoyl)benzotriazole mediated and *t*-BuOK promoted synthesis of 2-substituted quinolone 3-carboxylates

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ABSTRACT

2-Substituted quinolone 3-carboxylates were obtained in moderate to good yields by the reaction of *N*-(2-aminobenzoyl)benzotriazoles with β-ketoesters in the presence of *t*-BuOK in THF.

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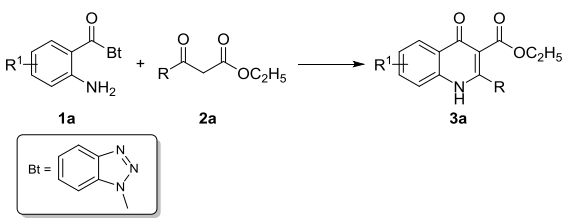
Quinolones are a widely employed series of synthetic antibacterial agents which have also been shown to possess various pharmacological activities such as anticonvulsant, antitumor and antiviral. These compounds have been widely used to treat genitourinary infections, prostatitis, respiratory diseases, gastroenteritis, sexually transmitted diseases, as well as skin and soft tissue infections.[1,2]

Most quinolone drugs contain the carboxylic acid moiety at the 3-position and the hydrolysis of 2-substituted quinolone-3-carboxylate derivatives **3** provides potential access to other analogues. In addition to being useful for the preparation of biologically important compounds, some activity studies have shown that the ester group at the 3-position of a quinolone ring is required for antibacterial activity[3] and replacement of this group with another group caused a decrease or loss in activity.[4a,b] Additionally, there have been reports that 2-substituted quinolone-3-carboxylates **3** are promising leads for the treatment of cancer[5] and AIDS.[6]

This motif has been synthesized using various methodologies including the reaction of i) anilines with various malonates;[7a-d] ii) benzonitriles with keto phosphorus ylides;[8] iii) isatoic anhydride with β-ketoesters;[7a, 9a,b] iv) *o*-isocyanobenzoates with magnesium enolates;[10] v) anthranilic acid with various reagents;[11a,b] vi) *N*-arylimines with various carbon nucleophiles[12a,b] and vii) 2-nitrobenzoic acid, activated by thionyl chloride[13a] or oxalyl chloride,[13b] with 1,3-dicarbonyl compounds (Scheme 1). These literature methods have several drawbacks such as long reaction times, multiple steps, toxic reagents, and starting materials which are difficult to synthesize. In the case of intramolecular electrophilic substitution, the regioselectivity of the reaction becomes a problem when using unsymmetrical substituted aniline derivatives.

N-(2-Aminobenzoyl)benzotriazoles, prepared from anthranilic acids and containing both free amino and active carbonyl groups, are stable reagents that have been utilised as versatile intermediates for the synthesis of anthranilic acid amides,[14] esters and thioesters[15] as well as heterocycles.[16] Similar to other *N*-acylbenzotriazole derivatives, *N*-(2-aminobenzoyl)benzotriazoles are easily prepared in crystalline form and are stable to moisture. As a continuation of our efforts to utilise *N*-(2-aminobenzoyl)benzotriazoles in synthesis, we herein describe a new protocol for the synthesis of 2-substituted quinolone-3-carboxylates **3**.

We initially synthesized a series of *N*-(2-aminobenzoyl)benzotriazoles from suitable anthranilic acids by stirring with benzotriazole in the presence of DCC at room temperature, according to the procedure developed by our group[14,15] (Scheme 3). To develop the optimum conditions, the reaction of *N*-(2-aminobenzoyl)benzotriazole **1a** with ethyl acetoacetate **2a** was chosen as a model system (Scheme 2) and a variety of reaction conditions were screened (Table 1). Initially, the reaction was carried out at RT and reflux in THF and DMF. It was found that in THF the yield increased from 30% at room temperature (Table 1, Entry 1) to 68% at reflux (Table 1, Entry 3). Next, we examined the effect of different bases and it was concluded that the use of *t*-BuOK in THF at reflux provided product **3a** in the highest yield.

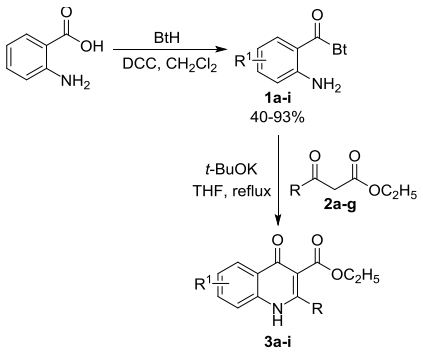


Scheme 2. Model reaction of *N*-(2-aminobenzoyl)benzotriazole with ethyl acetoacetate.

Table 1. Screening of reaction conditions.

Entry	Solvent	Base	Time (temp)	Yield of 3a (%)
1	THF	*t*-BuOK	Overnight (rt)	30
2	DMF	*t*-BuOK	Overnight (rt)	39
3	THF	*t*-BuOK	2 h (reflux)	68
4	DMF	*t*-BuOK	2 h (reflux)	55
5	THF	Na_2CO_3	2 h (reflux)	23
6	THF	NEt_3	2 h (reflux)	25

Having established the optimal reaction conditions, we then started to explore the generality of this reaction for the preparation of related quinolone carboxylates bearing different substituents (Table 2).



Scheme 3. Preparation of 2-substituted quinolone-3-carboxylates bearing different substituents.

of (i) – (vii).

Table 2. Synthesis of various 2-substituted quinolone-3-carboxylates.

Entry	Substrate		R	R^1	Product	Yield (%)
1	**1a**	**2a**	Me	-	**3a**	68 (67)[8a]
2	**1b**	**2b**	4-$MeOC_6H_4$	3-Me	**3b**	45
3	**1c**	**2c**	4-$NO_2C_6H_4$	4-Me	**3c**	42
4	**1d**	**2a**	Me	5-Me	**3d**	65
5	**1e**	**2d**	4-BrC_6H_4	4-F	**3e**	48
6	**1f**	**2e**	Ph	4-Cl	**3f**	72
7	**1g**	**2f**	4-MeC_6H_4	5-Br	**3g**	67
8	**1h**	**2g**	4-ClC_6H_4	5-I	**3h**	72
9	**1i**	**2a**	Me	3,5-Cl_2	**3i**	19

8a: Literature yield.

All 2-substituted quinolone-3-carboxylates were successfully synthesized in moderate to good yields, except **3i** which was isolated in only 19% yield (Table 2, entry 9). The reason for the low yield of **3i** may be due to the electronic effects of the chlorides in the aromatic ring. Except **3a**, all obtained compounds were novel and their structures identified by NMR spectroscopy. Because of the free acidic proton, these compounds have two possible tautomeric structures: 4-oxoquinoline and 4-hydroxyquinoline. In the ^{1}H-NMR spectra, a characteristic singlet resonance was observed around 12 ppm for all compounds, which could be assigned to either the NH or enolic OH proton.

In previously reported work, **3a** was prepared with two other examples of quinolone-3-carboxylates containing a free NH in the product, using *N*-hydroxysuccinimide as an activating agent.[11b] The products prepared in the literature work gave only poor to fair yields (13-34%) while all of the examples in the current work were considerably better in yield (19-72%) The ease and convenience of both methodologies are approximately the same and the current work represents a complementary alternative to prepare *N*-unsubstituted-2-substituted quinolone-3-carboxylates.

Consequently, we have developed a new method for the synthesis of 2-substituted quinolone-3-carboxylates using *N*-acylbenzotriazoles. This appears to be a suitable method for the preparation of quinolones with a variety of substituents at the 2-position and the benzene ring. Easily accessible starting compounds, mild reaction conditions and short reaction times are the advantages of the developed method.

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17. **Typical procedure for ethyl 4-hydroxy-2-methylquinoline-3-carboxylate (3a):** *N*-(2-Aminobenzoyl)benzotriazole **1a** (238 mg, 1 mmol) and ethyl acetoacetate **2a** (0.128 ml, 1 mmol) were stirred in anhydrous THF at room temperature for 1 h. *t*-BuOK (123 mg, 1.1 mmol) was added and the resulting mixture heated at reflux for two hours. Upon reaction completion, the THF was evaporated to provide the crude product which was first washed with water, then purified by flash column chromatography (silica gel, hexanes / EtOAc) to afford the desired product **3a** (156 mg, 68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.98 (br s, 1H), 8.03 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.37 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 173.9, 167.2, 149.4, 139.5, 132.7, 125.5, 124.9, 124.3, 118.4, 115.2, 60.8, 18.5, 14.5. Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; found: C, 66.92; H, 5.74; N, 6.09.