An Improved Protocol for the Synthesis of Quinoline-2,3-dicarboxylates under Neutral Conditions *via* Biomimetic Approach

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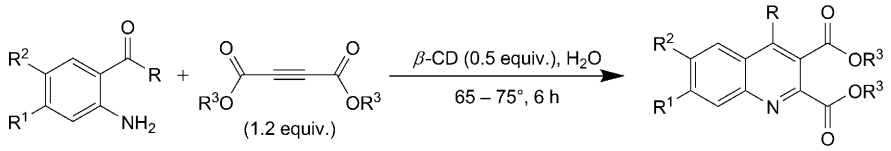
A mild and efficient protocol for synthesis of quinoline derivatives in aqueous medium under neutral conditions is described. The reaction proceeded smoothly in H_2O catalyzed by supramolecular catalyst β-CD. By this protocol, various quinoline derivatives were synthesized in excellent yields.

Introduction. – As part of our program to explore biomimetic approaches through supramolecular catalysis in promoting various organic transformations [1], we attempted to prepare biologically active heterocycles using β-cyclodextrin (β-CD) as a catalyst and H_2O as a reaction medium. However, the fundamental problem in performing organic reactions in H_2O is that many organic substrates are hydrophobic and are insoluble in H_2O. The aqueous reactions can be rendered more 'sophisticated' if they can be performed under supramolecular catalysis. Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities. They are torus-like macro-rings made up of glucopyranose units. They bind substrates selectively and catalyze chemical reactions by supramolecular catalysis involving the reversible formation of host–guest complexes with the substrates by noncovalent bonding as seen in enzyme-complexation processes [2]. The complexation depends on the size, shape, and hydrophobicity of the guest molecule. These attractive features of cyclodextrins in the biomimetic modeling of chemical reactions prompted us to investigate the synthesis of 4-substituted quinoline-2,3-dicarboxylates.

Results and Discussions. – Initially, the reaction between 2-aminobenzophenone and dimethyl acetylenedicarboxylate was carried out in H_2O catalyzed by β-CD resulting in the formation of dimethyl 4-phenylquinoline-2,3-dicarboxylate in one pot at 75° in 85% yield. When 50% of β-CD was used as the catalyst, the desired quinoline derivative was obtained in an almost quantitative yield, and reaction time was significantly short. In the absence of β-CD, the reaction did not take place. To check the generality of the reaction, various 2-amino carbonyl compounds were used as substrates, and all of the reactions proceeded to give the desired quinoline derivatives in yields, generally, $>80\%$. 5-Nitro-2-aminobenzophenone did not react, but traces of the product were isolated after longer reaction times. All these reactions also proceeded with diethyl acetylenedicarboxylate, but di(*tert*-butyl) acetylenedicarboxylate did not react under the present experimental conditions.

Table 1. *Synthesis of 4-Substituted Quinoline-2,3-dicarboxylates*[a]) *by Using β-Cyclodextrin* (*β*-CD) *under Neutral Conditions in Aqueous Medium*



Entry	R	R^1	R^2	R^3	Yield[b]) [%]
1	Me	H	H	Me	92
2	Me	H	H	Et	89
3	Ph	H	H	Me	85
4	Ph	H	H	Et	82
5	Ph	H	Cl	Me	83
6	Ph	H	Cl	Et	81
7	H	H	Cl	Me	94
8	H	H	Cl	Et	91
9	Ph	Br	H	Me	83
10	Ph	Br	H	Et	80
11	Me	MeO	MeO	Me	89
12	Me	MeO	MeO	Et	85
13	2-Cl–C_6H_4	H	Cl	Me	82
14	2-Cl–C_6H_4	H	Cl	Et	78
15	Me	$O–CH_2–O$		Me	88
16	Me	$O–CH_2–O$		Et	85

[a]) Structures of the products were confirmed by ^{1}H- and ^{13}C-NMR spectroscopy, and direct comparison with authentic samples. [b]) Yields of isolated products.

In general, all of the reactions were very clean. The compounds were purified by just passing them through a small silica-gel column. The results showed that the substitution played a significant role in governing the reactivity of the substrate. In general, reactions with 2-aminobenzophenones led to lower yields compared to 2-aminoacetophenones. However, 2-aminoacetophenones led to products in lower yields when compared to 2-amino-5-chlorobenzaldehyde. Among the 2-aminoacetophenones, unsubstituted 2-aminoacetophenone (*Table 1*, *Entries 1* and *2*) afforded good yields, and 4,5-methylenedioxy-2-aminoacetophenone (*Table 1*, *Entries 15* and *16*) resulted in lower yields. Similarly, reactions with substituted 2-aminobenzophenones gave lower yields compared to unsubstituted 2-aminobenzophenones. Finally, reactions of 2-aminophenones with dimethyl acetylenedicarboxylate (DMAD) resulted in higher yields when compared to those with diethyl acetylenedicarboxylates.

β-CD, being a supramolecular catalyst, catalyzes the reaction by forming inclusion complex with the substrates due to its hydrophobic cavity. Evidence for complexation between the 2-aminobenzophenone (**A**) and cyclodextrin is provided by ^{1}H-NMR spectroscopy as the most important technique for the characterization of inclusion complexes. Although all of the reactions were carried out with 0.5 equiv. of *β*-CD, complexation studies were undertaken with *β*-CD/2-aminobenzophenone 1:1 complex as a representative example. A comparative study of the shifts in cyclodextrin H-atoms

(host H-atoms) indicated that there is a downfield shift of H–C(3) (0.075) and H–C(5) (0.073) of cyclodextrin in the β-CD – **A** and β-CD – **A**-DMAD complex, respectively, compared to β-CD, indicating the formation of an inclusion complex of **A** with β-CD. This clearly demonstrates that 2-aminobenzophenone (**A**) is activated by β-CD, which promotes the reaction. β-Cyclodextrin was recovered in good quantity and reused for four times successively with sustained yields (*Table 2*).

Table 2. *Catalyst Recyclability*

Cycles	Yield [%]	Catalyst recovered [%]
Native	92	92
1	87	90
2	85	87
3	82	83

Conclusions. – We have presented an elegant, simple, and 'ecofriendly' protocol for the synthesis of quinoline derivatives in H_2O. This methodology under mild and neutral conditions overcomes the drawbacks of unwanted by-products, low yields, high temperatures, and problematic organic solvents.

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Experimental Part

General. All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from *Fluka* and *S. D. Fine Chemicals*. TLC: precoated silica-gel plates (*60 F_{254}*, 0.2-mm layer; *E. Merk*). M.p.: *Fischer–Johns* and *Barnstead Electrothermal* apparatus; uncorrected. ^{1}H-NMR Spectra: *Varian 200* or *Bruker 300* spectrometer; in $CDCl_3$; δ in ppm, J in Hz. MS: *QSTAR XL*, *LCQ-Ion Trap* spectrometer in *m/z*.

Typical Procedure for the Synthesis of Dimethyl 4-Phenylquinoline-2,3-dicarboxylate. β-CD (0.567 g, 0.5 mmol) was dissolved in H_2O (10 ml) by warming to 50° until a clear soln. was formed. Then, 2-aminobenzophenone (0.197 g, 1 mmol), was added dropwise, followed by dimethyl acetylenedicarboxylate (0.170 g, 1.2 mmol). The mixture was stirred at 75° until the reaction was complete (as monitored by TLC). The mixture was extracted with AcOEt, and the extract was filtered. The aq. layer was cooled to 5° to recover β-CD by filtration. The org. layer was dried (Na_2SO_4). The solvent was removed under reduced pressure, and the resulting product was further purified by column chromatography; yield 85% (*Table 1*, *Entry 3*). Bright yellow solid., M.p. 128–129° (lit. 129–130°). ^{1}H-NMR (300 MHz, $CDCl_3$): 8.39 (*d*, $J = 8.5$, 1 arom. H); 7.86–7.81 (*m*, 1 arom. H); 7.67–7.57 (*m*, 2 arom. H); 7.52–7.50 (*m*, 3 arom. H); 7.38–7.35 (*m*, 2 arom. H); 4.08 (*s*, COOMe); 3.64 (*s*, COOMe). ^{13}C-NMR (75 MHz, $CDCl_3$): 167.46; 165.34; 165.27; 148.30; 148.19; 146.84; 146.74; 144.70; 134.36; 131.12; 131.09; 130.42; 130.34; 129.23; 128.81; 128.22; 127.60; 127.13; 126.59; 53.44; 52.42. ESI-MS: 322 ($[M+H]^+$).

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