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Efficient synthesis of [1,3]oxazino[2,3-*a*]quinoline derivatives by a novel 1,4-dipolar cycloaddition involving a quinoline–DMAD zwitterion and carbonyl compounds

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Abstract—An efficient synthesis of [1,3]oxazino[2,3-*a*]quinoline derivatives via a three-component reaction of quinoline, DMAD and carbonyl compounds is described.

The Huisgen 1,3-dipolar cycloaddition constitutes a versatile protocol for the construction of a variety of five-membered heterocycles.[1,2] Huisgen's initiatives towards developing an analogous strategy for the synthesis of six-membered heterocycles using 1,4-dipoles,[3] however, received only limited attention. Except for isolated reports,[4,5] such reactions have remained largely unexploited.

In recent years, we have explored the reactivity of zwitterions derived from dimethyl acetylenedicarboxylate (DMAD) and nucleophiles such as phosphines,[6] isocyanides,[7] dimethoxycarbene,[8] nitrogen heterocycles[9] and *N*-heterocyclic carbenes (NHCs).[10] These studies have led to a number of interesting carbon–carbon bond forming reactions and heterocyclic constructions.[11] *Inter alia* we were intrigued by the drastically different reactivity patterns exhibited by the pyridine–DMAD zwitterion and the isoquinoline–DMAD zwitterion. Whereas the pyridine–DMAD zwitterion induced novel molecular rearrangements,[9a,b] the isoquinoline–DMAD zwitterion engaged exclusively in three component reactions.[9c–e] Thus we decided to investigate the reactivity of the zwitterion[12] generated from quinoline and DMAD towards electrophiles. To the best of our knowledge, this zwitterion has not been investigated from such a vantage point. In this Letter, we report the preliminary results of our investigations on trapping the quinoline–DMAD zwitterions with aldehydes and 1,2-diones leading to novel oxazinoquinoline derivatives.

In an initial experiment, a solution of 4-trifluoromethylbenzaldehyde **3a**, DMAD **2** and quinoline **1**, in dry toluene under argon, was taken in a sealed tube and the mixture was heated. Removal of the solvent followed by column chromatography afforded an inseparable diastereomeric mixture of [1,3]oxazino[2,3-*a*] quinoline derivatives **4a** and **5a** in 92% yield, in the ratio 4:1 (Scheme 1).

The major diastereomer **4a** was crystallized from the mixture and was subsequently characterized by spectroscopic analysis.[13] The methoxycarbonyl protons resonated as sharp singlets at δ 3.60 and 3.90, supporting the IR absorption at 1732 cm^{-1}. The ring junction proton signal was observed as a doublet at δ 5.24 ($J = 4.2$ Hz) and the benzylic proton displayed a singlet at δ 5.58. The signals due to the olefinic protons of the dihydroquinoline moiety were visible as a double doublet at δ 5.71 ($J_1 = 4.2$ Hz, $J_2 = 9.6$ Hz) and as a multiplet in the region δ 6.95–7.00. The ^{13}C NMR spectrum displayed the characteristic signals of the ester carbonyls at δ 163.9 and 165.3. Final confirmation of the structure and stereochemistry of **4a** was obtained from single crystal X-ray analysis (Fig. 1).[14]

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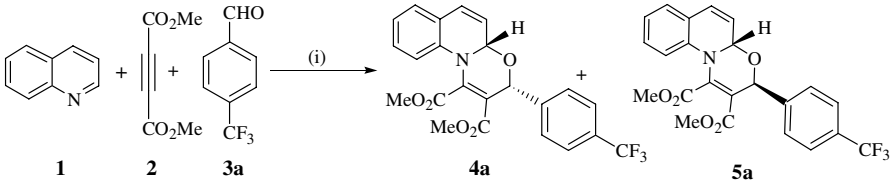


Scheme 1. Reagents and conditions: (i) Toluene, sealed tube, 110 °C, 12 h.

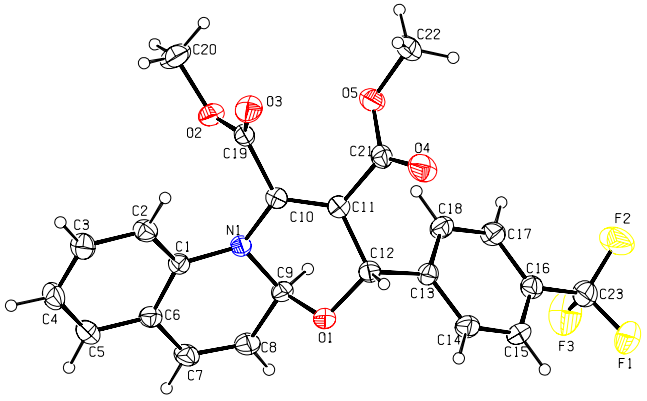


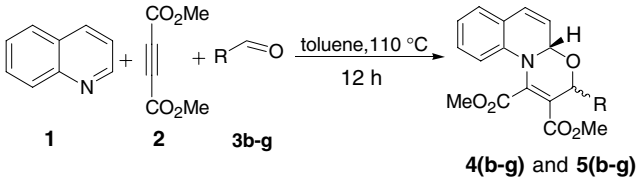
Figure 1. ORTEP diagram of compound **4a**.

Analogous reactions were observed with other aromatic aldehydes, and the results are presented in Table 1.

A mechanistic rationalization for the reaction is given in Scheme 2. The reaction can be considered to proceed via the initial formation of the 1,4-dipolar intermediate **6** from quinoline and DMAD, followed by its trapping with the aldehyde, to give the corresponding oxazinoquinoline derivative. However, a two-step process involving the intermediacy of alkoxide **8** cannot be ruled out.

In view of the interesting results obtained by the trapping of quinoline–DMAD zwitterions with aldehydes, we next focussed our attention on reactions with 1,2-diones. In an initial experiment, 2,2′-thenil **9a**, DMAD

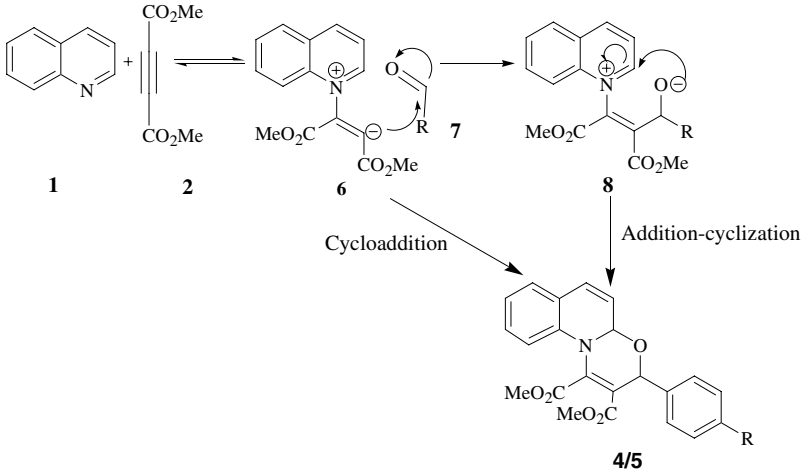
Table 1. Addition of the quinoline–DMAD zwitterions to aldehydes



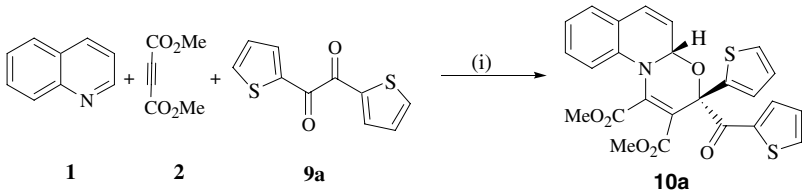
Entry	R	Product	Ratio	Yield (%)
1	3,4-Difluorophenyl	**4b/5b**	6:1	74
2	3,4-Dichlorophenyl	**4c/5c**	4:1	72
3	4-Bromophenyl	**4d/5d**	4:1	82
4	4-Chlorophenyl	**4e/5e**	4:1	78
5	2-Chlorophenyl	**4f/5f**	6:1	45
6	3-Nitrophenyl	**4g/5g**	6:1	75
7	4-Nitrophenyl	**4h/5h**	6:1	88
8	2-Naphthyl	**4i/5i**	4:1	77
9	2-Furyl	**4j/5j**	4:1	29
10	2-Thienyl	**4k/5k**	4:1	35
11	4-Methoxyphenyl	**4l/5l**	2:1	30

2 and quinoline **1** were heated in a sealed tube in dry toluene. Interestingly, the reaction afforded a single diastereomer **10a** in 52% yield (Scheme 3).

The structure of product **10a** was ascertained by spectroscopic methods.[15] In the ^{1}H NMR spectrum, signals due to the methoxycarbonyl protons were observed as sharp singlets at δ 3.77 and 3.83. The ring junction proton was discernible as a doublet at δ 5.40 ($J = 4.4$ Hz). The olefinic protons of the dihydroquinoline moiety were visible as a double doublet at δ 5.83 ($J_1 = 4.4$ Hz, $J_2 = 9.8$ Hz)



Scheme 2.



Scheme 3. Reagents and conditions: (i) Toluene, sealed tube, 110 °C, 12 h.

and as a multiplet in the region δ 6.71–6.68. The ^{13}C keto carbonyl resonance signal occurred at δ 188.1 and the methoxycarbonyls at δ 165.2 and 163.6. In the IR spectrum, the ketone carbonyl absorption was observed at 1720 cm^{-1} and the ester carbonyl absorption at 1737 cm^{-1}. Conclusive evidence for the structure and stereochemistry of **10a** was obtained by single crystal X-ray analysis (Fig. 2).[14]

The reaction was applicable to a number of other diaryl 1,2-diones **9b–h**, affording the oxazinoquinoline derivatives **10b–h** in moderate yields (Table 2).

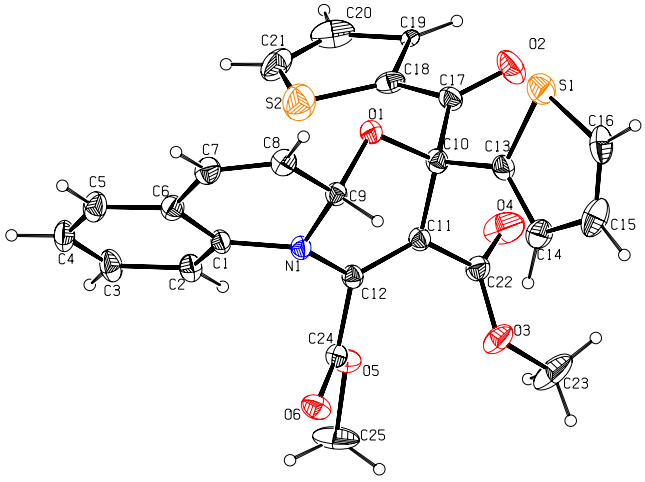
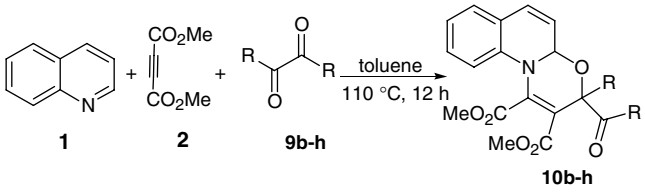


Figure 2. ORTEP diagram of compound **10a**.

Table 2. Addition of the quinoline–DMAD zwitterions to 1,2-diones



Entry	R	Product	Yield (%)
1	4-Fluorophenyl	**10b**	65[a]
2	4-Trifluoromethylphenyl	**10c**	62[a]
3	3,4-Difluorophenyl	**10d**	61[a]
4	3,4-Dichlorophenyl	**10e**	61[a]
5	4-Chlorophenyl	**10f**	60[a]
6	Phenyl	**10g**	55[a] (70)[b]
7	4-Methylphenyl	**10h**	53[a] (70)[b]

[a] Isolated yield.
[b] Yield based on recovered starting material.

A mechanistic postulate analogous to that suggested for the reaction of aldehydes can be invoked to explain the formation of oxazinoquinoline derivatives **10a–h**. Further work will be undertaken to examine the scope of the reactions described herein.

In conclusion, we have devised an efficient strategy for the synthesis of a variety of oxazinoquinoline derivatives.

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13. *Representative experimental procedure and spectroscopic data for* **4a**: 4-Trifluoromethylbenzaldehyde **3a** (76.61 mg, 0.44 mmol), quinoline **1** (68.45 mg, 0.53 mmol) and dimethyl acetylenedicarboxylate **2** (75.26 mg, 0.53 mmol) were taken in dry toluene (3 mL) in a sealed tube and heated at 110 °C for 12 h. Removal of the solvent followed by purification of the reaction mixture by column chromatography (silica gel, 100–200 mesh; 90:10 *n*-hexane/ethyl acetate) afforded an inseparable diastereomeric mixture of the oxazinoquinoline derivatives (409.5 mg, 92%) as a yellow solid which on recrystallization from DCM/hexane (1:1) furnished **4a** as a yellow crystalline solid. Mp = 158–160 °C. IR (KBr) ν_{max}: 2960, 1732, 1607, 1499, 1324, 1246, 1160, 1126, 1070, 1014 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 8.1$ Hz, 2H), 7.23 (t, $J = 7.2$ Hz, 2H), 7.00–6.95 (m, 1H), 6.82–6.74 (m, 2H), 5.71 (dd, $J_1 = 4.2$ Hz, $J_2 = 9.6$ Hz, 1H), 5.58 (s, 1H), 5.24 (d, $J = 4.2$ Hz, 1H), 3.90 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 163.9, 143.8, 139.8, 135.8, 129.9, 128.7, 128.3, 125.7, 122.2, 121.5, 118.7, 114.8, 112.1, 108.2, 106.3, 96.1, 77.3, 76.8, 76.4, 74.0, 53.1, 52.2. HRMS (EI) *m*/*z* calcd for $C_{23}H_{18}F_3NO_5$: 445.1137, found: 445.1131.
14. Single crystal X-ray data for **4a** and **10a** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 634543 and 634544, respectively.
15. *Representative experimental procedure and spectroscopic data for* **10a**: 2,2′-Thenil **9a** (97.79 mg, 0.44 mmol), quinoline **1** (68.45 mg, 0.53 mmol) and dimethyl acetylenedicarboxylate **2** (75.26 mg, 0.53 mmol) were taken in dry toluene (3 mL) in a sealed tube and heated at 110 °C for 12 h. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography (silica gel, 100–200 mesh; 90:10 *n*-hexane/ethyl acetate) to give the oxazinoquinoline derivative (256.4 mg, 52%) as a yellow solid. **10a** was recrystallized from DCM/hexane (1:1). Mp = 134–137 °C. IR (KBr) ν_{max}: 3680, 3018, 3012, 2432, 2399, 1737, 1720, 1521, 1496, 1477, 1423. ^1H NMR (300 MHz, $CDCl_3$): δ 7.81–7.79 (m, 1H), 7.63–7.61 (m, 1H), 7.24–7.14 (m, 3H), 7.02–6.99 (m, 3H), 6.85–6.81 (m, 2H), 6.71–6.68 (m, 1H), 5.83 (dd, $J_1 = 4.4$ Hz, $J_2 = 9.8$ Hz, 1H), 5.40 (d, $J = 4.4$ Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.1, 165.2, 163.6, 142.1, 138.5, 137.8, 136.3, 136.0, 135.2, 129.9, 129.7, 129.0, 128.3, 127.9, 127.8, 126.4, 126.2, 125.7, 121.9, 120.9, 84.1, 78.4, 53.1, 52.1, 51.8. HRMS (EI) *m*/*z* calcd for $C_{25}H_{19}NO_6S_2$: 493.0654, found: 493.0651.