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The reaction of isoquinoline and dimethyl acetylenedicarboxylate with 1,2- and 1,4-benzoquinones: a novel synthesis of spiro[1,3]oxazino[2,3-*a*]isoquinolines

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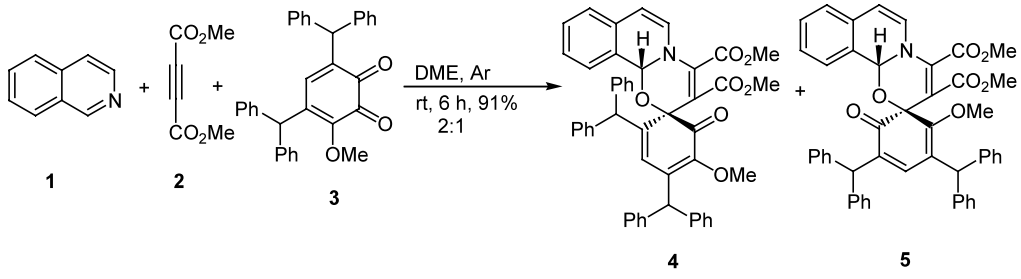
Abstract—The 1,4-dipolar intermediate generated by the addition of isoquinoline to dimethyl acetylenedicarboxylate is trapped by 1,2- and 1,4-benzoquinones to afford spiro[1,3]oxazino[2,3-*a*]isoquinoline derivatives in high yields.

The pronounced reactivity of nitrogen-containing heterocycles towards dimethyl acetylenedicarboxylate (DMAD) is well documented.[1] The reaction generally involves the initial addition of the *N*-heterocycle to DMAD to form a dipolar intermediate, which undergoes further reaction with DMAD leading to a variety of complex heterocyclic compounds; such reactions have been the subject of detailed investigations by a number of research groups.[2–5]

In his pioneering work, Huisgen has shown that the reaction of isoquinoline and DMAD proceeds through a 1,4-dipolar intermediate, by trapping it with external dipolarophiles such as phenyl isocyanate, diethyl mesoxalate and dimethyl azodicarboxylate.[6] The utility of this reaction for the synthesis of six-membered heterocycles however has not been explored so far. Recently we have employed this strategy to devise a novel three component condensation reaction leading to the diastereoselective synthesis of 2*H*-pyrimido[2,1-*a*]-isoquinoline derivatives.[7] In the context of our experience in the dipolar cycloaddition reactions of quinonoid compounds,[8] it was surmised that the Huisgen 1,4-dipole (vide supra) was likely to undergo cycloaddition to quinones leading to novel spirofused heterocycles. We therefore initiated an investigation of the reaction of isoquinoline and DMAD with 1,2- and 1,4-benzoquinones and our preliminary results validating the assumption are presented here.

In our initial experiment, the reaction of isoquinoline and DMAD with 3-methoxy-4,6-bis(diphenylmethyl)-1,2-benzoquinone **3** in DME at room temperature afforded spiro[1,3]oxazino[2,3-*a*]isoquinoline derivatives **4** and **5** as a mixture of regioisomers in the ratio 2:1 in 91% yield (Scheme 1).



Scheme 1.

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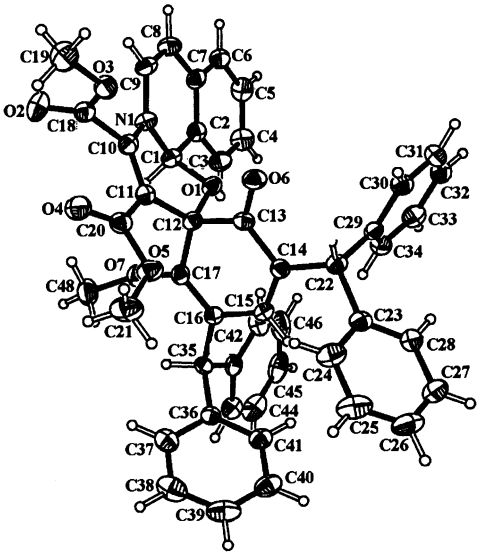
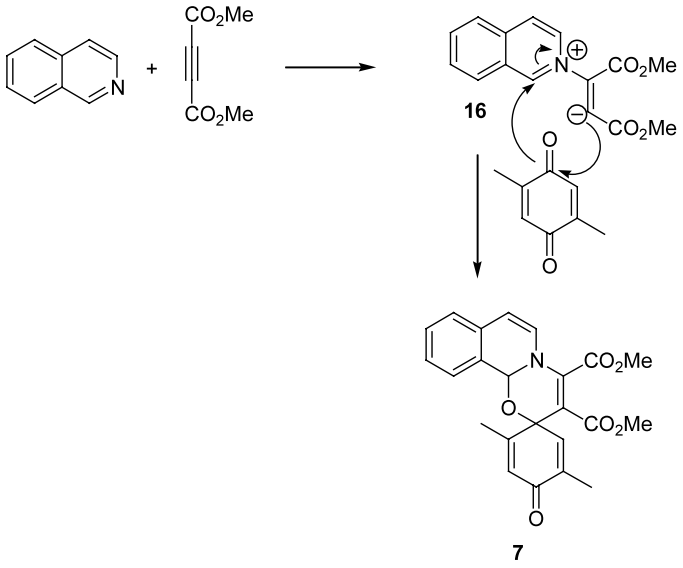


Figure 1. ORTEP diagram of **5**.



Scheme 3.

The IR spectra of **4** and **5** showed strong absorptions at 1742 and 1708 cm^{-1} due to ester carbonyls; the enone carbonyl was discernible at 1667 cm^{-1}. In the ^1H NMR spectrum of **4** signals due to the three methoxy groups were visible at δ 3.94, 3.54 and 3.40; the corresponding signals for **5** were observed at δ 3.90, 3.64 and 3.47. The ring junction proton of **4** was discernible as a singlet at δ 6.50; the corresponding signal for **5** was seen as singlet at δ 6.68. In the ^{13}C NMR spectrum of **4**, the characteristic signal for the spirocarbon was observed at δ 78.22, whereas in the spectrum of **5**, it was at δ 80.92. Finally, the structure and the stereochemistry of the regioisomer **5** was established unambiguously by single-crystal X-ray analysis (Fig. 1).[9]

Similar reactivity was also observed with 1,4-benzoquinones. Thus, 2,5-dimethyl-1,4-benzoquinone **6** when treated with DMAD in presence of isoquinoline gave 76% of the spiro[1,3]oxazino[2,3-*a*]isoquinoline derivative **7** (Scheme 2).[10]

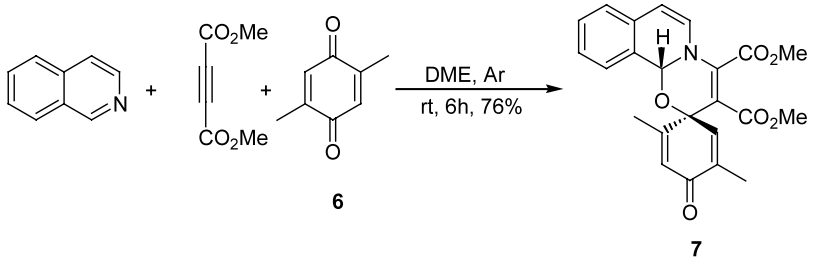
Analogous results were obtained with a number of other quinones and the results are summarised in Table 1.[11]

Mechanistically the reaction can be considered to involve cycloaddition of the initially formed 1,4-dipolar intermediate **16**, to quinone carbonyl to form the adduct **7** as shown in Scheme 3.

In conclusion, we have observed a novel three-component condensation reaction that constitutes an easy and effective one-pot synthesis of highly substituted spiro[1,3]oxazino[2,3-*a*]isoquinoline derivatives; such compounds are known to possess therapeutically important biological activities.[12]

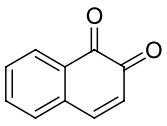
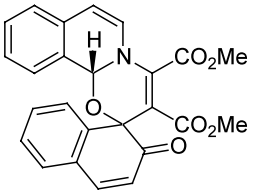
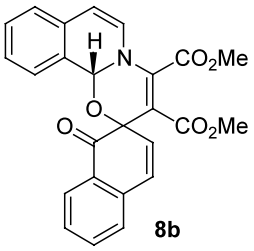
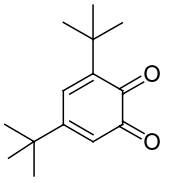
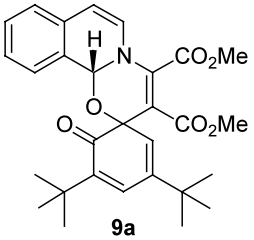
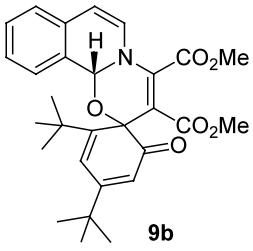
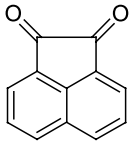
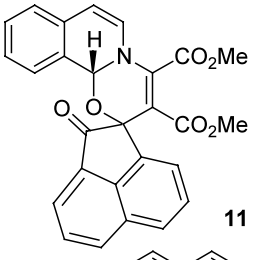
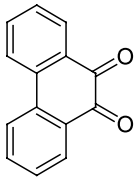
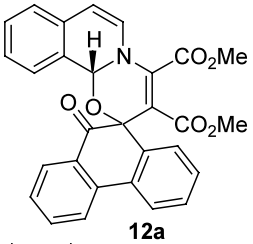
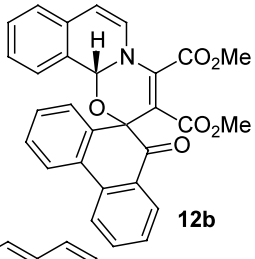
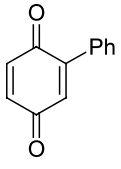
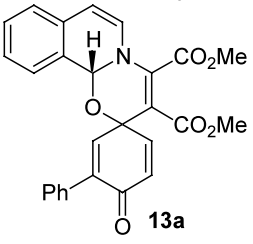
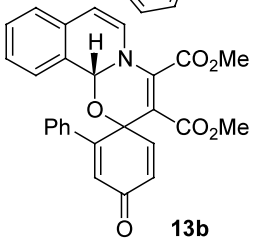
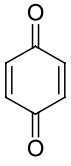
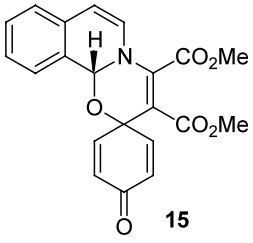
Acknowledgements

S.A.R. and B.A.T. thank CSIR, New Delhi, for research fellowships. The authors also thank Mrs. Soumini Mathew for high-resolution NMR spectra and Mrs. Viji S. for elemental analysis.



Scheme 2.

Table 1. Reaction of isoquinoline and DMAD with quinones

Entry	Quinone	Products	Ratio [a]	Yield(%) [b]
1	 **8**	 **8a**  **8b**	1:1	62
2	 **9**	 **9a**  **9b**	1:2	85
3	 **10**	 **11**		53
4	 **12**	 **12a**  **12b**	1:1	75
5	 **13**	 **13a**  **13b**	2:1	90
6	 **14**	 **15**		75

Reaction conditions = DME, Ar, rt, 6 h, a = ratio of regioisomers, b = isolated yield

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9. Crystal data for **5**: C_{48} H_{39} N O_7, M. 741.80, triclinic, space group *P*-1, unit cell dimensions $a=11.9289(8)$, $b=13.0369(9)$, $c=13.6567(9)$ Å, $\alpha=97.369(5)$, $\beta=115.503(4)$, $\gamma=90.242(5)°$, *R* indices (all data) $R_1=0.1311$, $wR_2=0.1294$, volume 2, $Z=1896.9(2)$ $Å^3$, $D_{calcd}=1.299$ Mg/m^3. Absorption coefficient $=0.087$ mm^{-1}, $\lambda=0.71073$ Å, reflections collected 34089 (CCDC 197575).
10. Typical experimental procedure and spectral data of dimethyl 2,5-dimethyl-4-oxo-spiro[cyclohexa-2,5-diene-1,2′-[2*H*,11b*H*][1,3]oxazino[2,3-*a*]isoquinoline]-3′,4′-dicarboxylate **7**: Isoquinoline (0.062 ml, 0.53 mmol) was added to a stirred solution of 2,5-dimethyl-1,4-benzoquinone (72 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME under argon atmosphere at rt and the reaction mixture was stirred for 3 h. The solvent was removed under vacuum, followed by column chromatography on silica gel using hexane–ethyl acetate (80:20) gave the product **7** as a yellow solid. Mp 168–170°C; IR (KBr) cm^{-1}: 2955, 1742, 1721, 1681, 1647, 1593, 1566, 1438, 1283, 1236, 1148: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 3H), 7.13 (t, $J=8.10$ Hz, 1H), 6.89 (s, 1H), 6.39 (dd, $J=7.69$, 14.15 Hz, 1H), 6.21 (m, 1H), 6.06 (s, 1H), 5.83 (q, $J=7.74$ Hz, 1H), 3.94 (s, 3H), 3.61 (s, 3H), 1.96 (s, 3H), 1.83 (s, 3H): ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.11, 163.94, 163.27, 156.36, 153.70, 143.59, 138.66, 134.65, 129.71, 129.05, 127.51, 127.18, 125.99, 125.30, 123.60, 109.93, 104. 89, 104.66, 79.34, 53.33, 52.03, 17.45, 15.67. Anal. calcd for $C_{23}H_{21}NO_6$: C, 67.80; H, 5.20; N, 3.44%. Found C, 67.52; H, 5.19; N, 3.82%.
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