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Tetrahedron Letters 45 (2004) 8257–8259
Tetrahedron Letters

Easy access to *N*-aryl, *N*-heteroarylbenzoxazolinones and 4-aza analogues via Diels–Alder cycloaddition reactions

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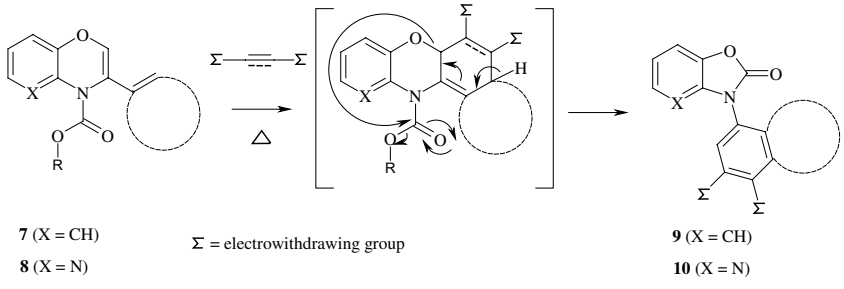
Received 2 July 2004; revised 27 August 2004; accepted 30 August 2004

Abstract—An improved method for the synthesis of *N*-aryl, *N*-heteroarylbenzoxazolinones and their 4-aza analogues is described. The process involves the Diels–Alder cycloaddition of benzoxazinic or pyridoxazinic dienic systems with dienophiles as a key step.

The benzoxazolinone moiety is present in a considerable number of derivatives exhibiting various biological activities.[1] The nitrogen atom generally bears substituted linear or branched alkyl chains. On the other hand, *N*-arylbenzoxazolinones are rarely reported in the literature. In fact, their synthesis from appropriate hydroxydiarylamines[2] or by aromatic nucleophilic substitutions[3] is quite easy but not versatile enough nor satisfactory in terms of molecular diversity. Furthermore, the preparation of such aza analogues as 3-aryloxazolo[4,5-*b*]pyridine-2(3H)-ones, obtained by a 1,3-dipolar cycloaddition reaction of pyridine N-oxides with arylisocyanates, gives very poor yields.[4]

In the course of a work devoted to the synthesis of complex heteropolycyclic derivatives with potential biological activity, we used a Diels–Alder reaction involving dienic systems **7** and **8** as a key step. These derivatives, which possess a benzoxazinic or pyridoxazinic subunit, were easily obtained in high yield via palladium-catalysed cross-coupling reactions from the corresponding lactams.[5]

We think that **7** and **8**, depending on which *N*-protecting carbamate is chosen, could constitute ideal precursors for the direct synthesis of *N*-aryl, *N*-heteroarylbenzoxazolinones and their 4-aza analogues via a Diels–Alder reaction. Indeed, it was possible to observe first the cycloadduct ring opening (spontaneously or in the presence of a base with an ultimate air oxidation step), which led to the formation of the *N*-aryl or *N*-heteroaryl ring. This was followed by the formation of the



Scheme 1.

Keywords: Benzoxazolinones; Benzoxazines; Pyridoxazines; Diels–Alder cycloaddition.
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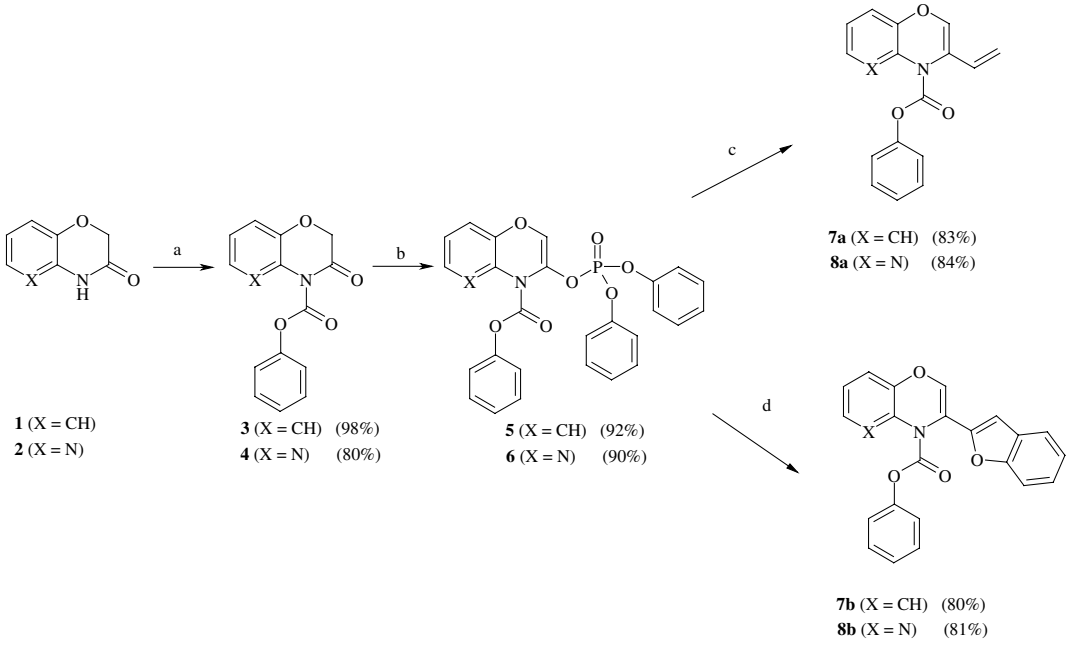
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2004.08.162

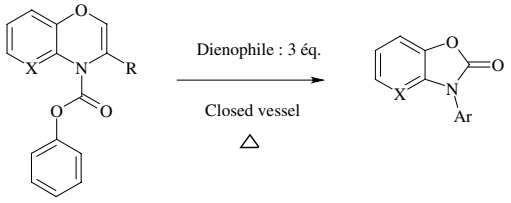
oxazolinone moiety via an intramolecular attack of the carbamate by the phenolic leaving group (Scheme 1).

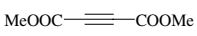
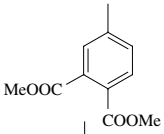
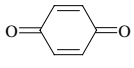
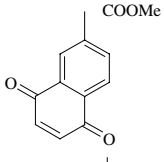
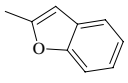
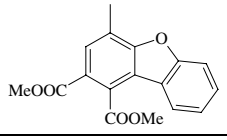
Depending on the nature of the dienophile and dienic systems, the number of benzoxazolinones or 4-aza ana-



Scheme 2. Synthesis of dienic systems: (a) *n*-BuLi, ClCOOPh, THF, −78 °C; (b) LDA, $ClP(O)(OPh)_2$, THF, −78 °C; (c) vinyltributyltin, $Pd(PPh_3)_4$, LiCl, THF, reflux; (d) benzo[*b*]furylboronic acid, $PdCl_2(PPh_3)_2$, Na_2CO_3 2 M, THF, reflux.

Table 1. Synthesis of benzoxazolinones **9a**,**b** and pyridoxazolinones **10a**,**b**



R	Dienophile	Ar	Products	X	Temp (°C)	Time (h)	Yield (%)[c,d]
			**9a–1**	CH	95	3	85
			10a–1	N	70	2	85
			10a–1	N	20	96	85
			**9a–2**	CH	70	1	90[a,b]
			10a–2	N	70	1	70[b]
			**9b–1**	CH	95	24	60
			10b–1	N	95	5	41

[a] After treatment by triethylamine in dichloromethane.
[b] Diels–Alder reaction performed in the presence of toluene.
[c] Isolated yields.
[d] All isolated compounds afforded satisfactory elemental analysis and spectral data.

logues obtained can vary greatly. Taking a phenyl carbamate as the *N*-protecting group seemed to be the most appropriate choice to reach our goal.

We prepared 3-substituted benzoxazines **7a**,**b** and 3-substituted pyridoxazines **8a**,**b** via Stille or Suzuki coupling reactions following the synthetic approach we previously described[5] (Scheme 2).

Vinylphosphates **5** and **6** were thus obtained in two steps from commercially available lactams **1** and **2**, respectively, in 90% and 72% yields. These derivatives were then engaged in palladium-catalysed cross-coupling reactions following the conditions reported in Scheme 2.

The four different dienic systems were then engaged, most of the time without using any solvents, in Diels–Alder reactions using dimethylacetylene dicarboxylate or 1,4-benzoquinone as typical dienophiles.[6] The expected reactions effectively occurred and the benzoxazolinones **9a**,**b** and pyridoxazolinones **10a**,**b** were obtained in fair to good yields (Table 1).

In some cases (e.g., product **9a**–**2**) the intermediate cycloadduct was isolated and it was necessary to add first some dichloromethane at room temperature, then a few drops of triethylamine to observe the completion of the reaction. In the aza-series the cycloadducts were more sensitive and opened spontaneously yielding to the required derivatives. With dienes **7b** and **8b** each bearing a benzofuran subunit, the Diels–Alder reaction was obviously more difficult to complete, the reaction took longer and the yields were lower than in the other cases.

In conclusion, this paper describes an efficient synthesis of *N*-aryl, *N*-heteroarylbenzoxazolinones and 4-aza analogues. Considering the diversity of the accessible dienic and dienophile systems our method allows an easy access to a great variety of heterocycles, which offer high potentialities for medicinal chemistry or agrochemical applications.

In this context, further studies directed towards the synthesis of such derivatives are in progress in our laboratory and will be reported in due course.

References and notes

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6. Standard procedure: Phosphate **5** (501 mg, 1 mmol) and tributyl(vinyl)tin (634 mg, 2 mmol) were dissolved in THF (3 mL). Tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol) and lithium chloride (127 mg, 3 mmol) were added and the reaction was refluxed for 2 h. After concentration the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous solution of sodium chloride, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (6/4) to give the desired product **7a** (232 mg, 83%) as a yellow solid. Mp 70–72 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ ppm 5.16 (dd, 1H, CH_2 vinyl, J_{cis} = 11 Hz, J_{gem} = 1 Hz), 5.41 (dd, 1H, CH_2 vinyl, J_{trans} = 17.5 Hz, J_{gem} = 1 Hz), 6.31 (dd, 1H, CH vinyl, J_{cis} = 11 Hz, J_{trans} = 17.5 Hz), 6.77 (s, 1H, H_2), 6.97–7.38 (m, 8H), 7.62 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ ppm 113.20 (CH_2), 116.65 (CH), 121.95 (2CH), 124.4 (CH), 125.35 (C), 125.80 (CH), 126.30 (CH), 127.20 (CH), 128.25 (CH), 128.80 (C), 129.85 (2CH), 140.25 (CH), 151.30 (C), 152.50 (C). MS: *m*/*z* = 280 (M+1).
Dienic compound **7a** (187 mg, 0.67 mmol) and dimethylacetylene dicarboxylate (250 μL, 2.0 mmol) were mixed then heated at 95 °C for 3 h in a closed vessel. After cooling to room temperature, the mixture was directly purified by flash chromatography (petroleum ether/ethyl acetate: 7/3) to afford *N*-arylbenzoxazolinone **9a**–**1** (186 mg, 85%) as a white solid. Mp 85 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ ppm 3.94 and 3.95 (2s, 6H, $2CH_3O$), 7.13–7.32 (m, 4H), 7.81 (dd, 1H, H_5, $J_{5,6}$ = 8.5 Hz, $J_{3,5}$ = 2 Hz), 7.91–7.97 (m, 2H, H_3 and H_6); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ ppm 53.00 and 53.05 ($2CH_3$); 109.45 (CH), 110.70 (CH), 123.95 (CH), 124.35 (CH), 124.65 (CH), 130.70 (CH), 126.85 (CH), 130.00 (C),131.10 (C),133.90 (C), 136.30 (C), 142.75 (C), 152.55 (C), 166.90 (C), 167.00 (C). MS: *m*/*z* = 328 (M+1).