

Modified Knoevenagel–Stobbe Preparation of Substituted Pyridines: a New Approach to Streptonigrinoids

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Dihydropyrans obtained by cyclocondensation of aromatic enones with vinyl ethers are transformed into pyridines by treatment with hydroxylamine hydrochloride.

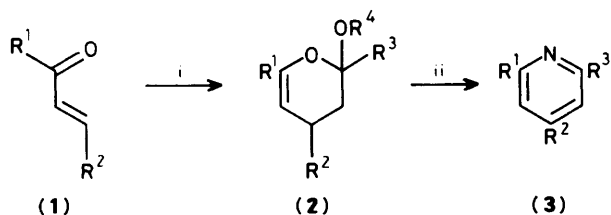
We describe here a modified Knoevenagel–Stobbe¹ preparation of 2,4-disubstituted pyridines. It was found that 1,5-dicarbonyl compounds required for that reaction may be obtained, in protected form, by the recently developed

cycloaddition of enones/enals to vinyl ethers,² and used as such. Furthermore, employment of such protected substrates often permits a cleaner conversion than normally possible with starting materials incorporating an expressed 1,5-dicarbonyl

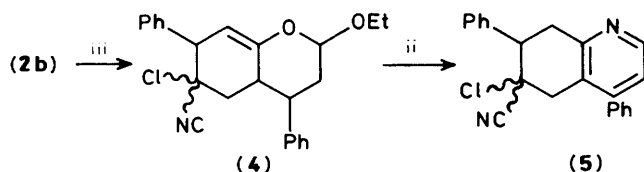
Table 1. Yields for the reactions in Scheme 1.

Enone(1)	R ¹ =	R ² =	(2) R ³ =	R ⁴ =	Yield (%) ^a	Yield (%) of (3)
(a)	Phenyl	Phenyl	H	Et	100	81 ^b
(a)	Phenyl	Phenyl	Me	Me	97	85 ^c
(b)	(<i>E</i>)-β-Styryl	Phenyl	H	Et	100	84 ^c
(c)	2-Furyl	Phenyl	H	Et	91	95 ^c
(d)	Phenyl	Cyclohexyl	H	Et	100	40 ^c
(e)	Phenyl	n-Nonyl	H	Et	100	25 ^b
(f)	Phenyl	2-Furyl	H	Et	70	61 ^c

^a Of crude product. ^b Of chromatographed products. ^c Of pure hydrochloride.



Scheme 1. Reagents and conditions: i, EtOCH=CH₂ (10 equiv.), Yb(fod)₃ (5 mol %), (CH₂Cl)₂, reflux 3–30 h; ii, NH₂OH·HCl, reflux 10 h.



Scheme 2. Reagents and conditions: i, ii as Scheme 1; iii, CH₂=CHCICN, benzene, reflux.

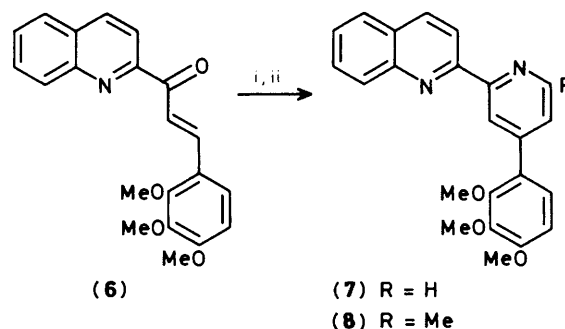
functionality. Table 1 shows representative examples. The enones (1)[†] were subjected to cyclocondensation with ethyl vinyl ether or with 2-methoxypropene.[‡] The adducts from ethyl vinyl ether were formed almost exclusively as the *cis*-stereoisomers, suggesting high *endo*-selectivity in the reaction. By contrast, 2-methoxypropene produced a 1:1 mixture of diastereometric cycloadducts. Without further purification, the dihydropyrans (2) were refluxed in ethanol with 2 equiv. of hydroxylamine hydrochloride,⁴ whereupon conversion into the corresponding pyridines occurred.[§]

In most cases, the pyridines were conveniently isolated, in pure form, by precipitation from ethyl ether, as the rather hygroscopic hydrochlorides (HCl gas). Dienones such as dibenzylidene acetone also participated in the reaction, affording vinylpyridines [cf. (3b)]. However, no regioselectivity was found in the reaction of unsymmetrical dienones with vinyl ethers. For instance, 1-(4-nitrophenyl)-5-(2-furyl)pent-1,4-dien-3-one afforded 1:1 ratios of cycloadducts. On the other hand, cycloadducts type (2b) incorporate an electron-rich diene system capable of reacting with typical dienophiles. Products of such 'double cycloadditions,' e.g. (4) are con-

[†] The enones (1d) and (e) were prepared by Wittig reactions of benzolymethylene(triphenyl)phosphorane with appropriate aldehydes. The others were made by the procedure of Kohler and Chadwell³ using the appropriate methyl ketone/aldehyde combination.

[‡] Two limitations of this chemistry were uncovered. The enones (1) failed to condense with cyclic vinyl ethers such as dihydropyran or dihydrofuran. Moreover, it appeared that at least one aryl group had to be present in conjugation with the enone carbonyl for combination with the vinyl ether to occur. We were thus unable to induce reaction between vinyl ethers and e.g. (*E*)-tridec-3-en-2-one, or (*E*)-4-cyclohexylbut-3-en-2-one.

[§] All new compounds described herein gave satisfactory analytical data.



Scheme 3. Reagents and conditions: i, ii as Scheme 1.

verted into annelated pyridines of type (5) by hydroxylamine hydrochloride (42%; mixture of stereoisomers).

It was surmised that the new technique might be applied to the synthesis of streptonigrin-like pyridines.⁵ In order to explore that possibility, the enone (6)[¶] was subjected to the foregoing conditions. Indeed, conversion into compounds (7) and (8) occurred readily. The pyridines (7) and (8) required purification by column chromatography, a fact that contributed to lower their yields to a moderate 25–30%. Nonetheless, ready entry into the streptonigrin system had been demonstrated.

Implications and ramifications of the present results are being investigated.

We are grateful to the Robert A. Welch Foundation (C-1007) and to the National Science Foundation (CHE-8708130) for financial support.

Received, 19th May 1988; Com. 8/01987H

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[¶] Prepared from 2-acetylquinoline.⁶