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STEREOSELECTIVE SYNTHESIS OF PIPECOLIC ACID DERIVATIVES USING AZA-DIELS-ALDER REACTIONS

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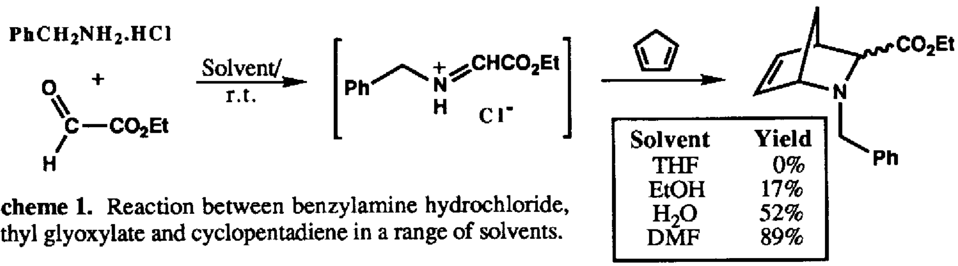
Summary. Pipecolic acid derivatives can be prepared by the aza-Diels-Alder reaction of dienes with the iminium salt derived from benzylamine and ethyl glyoxylate in DMF; the presence of a catalytic quantity of water is essential, and acyclic dienes react with high regio- and dia-stereoselectivity.

The Diels-Alder reaction of an imine with a diene offers a short and potentially stereospecific route to a wide range of piperidine derivatives.[1] Disappointingly, many imines fail to participate in these (4+2) cyclo-additions, although two observations have extended the scope of these reactions considerably: the first is that highly electron deficient imines, particularly the protonated iminium salts, are much more effective dienophiles;[1,2] the second is that the reactions are often dramatically accelerated when carried out under aqueous conditions.[2] Nevertheless, the application of this chemistry to the synthesis of pipecolic acid derivatives has been limited,[3] and we descibe herein a reliable one-pot procedure that gives direct access to these important compounds.

In an attempt to extend the utility of the aza-Diels-Alder chemistry, we initially carried out a detailed study of the reaction between cyclopentadiene and the imine derived (*in situ*) from benzylamine hydrochloride and ethyl glyoxylate[4].



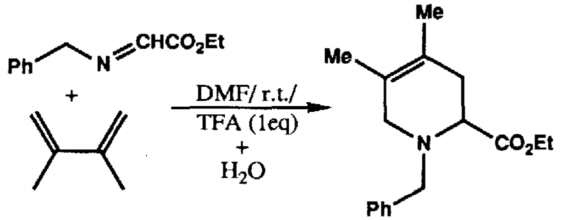
Solvent	Yield
THF	0%
EtOH	17%
H_2O	52%
DMF	89%

Scheme 1. Reaction between benzylamine hydrochloride, ethyl glyoxylate and cyclopentadiene in a range of solvents.

The yield of cyclo-adduct was extremely dependent on solvent, as indicated in Scheme 1, with DMF giving the best results (89%). With the hope of boosting the yield still further, molecular sieves were added in order to assist formation of the imine; to our surprise, none of the expected adduct was formed, and the imine ($PhCH_2N=CHCO_2Et$) was isolated from the reaction mixture in good yield. Further experiments revealed that the presence of water was essential for the cyclo-addition reaction to proceed.

With an effective set of reaction conditions in hand,[5] we explored whether other dienes might react successfully with benzylamine/ethyl glyoxylate; these results are summarised in the Table. With the exception of the very unreactive 1,4-diphenylbutadiene (which was recovered intact), and Danishefsky's diene (which was rapidly destroyed under the reaction conditions), the cyclo-adducts could be isolated in moderate yields from the simple one-pot procedure.

Particularly notable was the high regio- and diastereo-selectivity observed with the acyclic dienes, emphasising the value of Diels-Alder chemistry in the synthesis of these heterocyclic molecules. For example, the adduct with *trans*-penta-1,3-diene was composed of a single regio-isomer in 86% diastereomeric excess (d.e.). It would appear that "o,p"-substituted piperidines are generally produced, and that the stereochemistry results from a concerted cyclo-addition *via* an endo transition state.



H_2O (mol%)	Yield
1	94%
10	94%
100	29%
1000	9%

Scheme 2. Reaction between 2,3-dimethylbutadiene and $PhCH_2N=CHCO_2Et$

An additional series of reactions between 2,3-dimethylbutadiene and the isolated imine ($PhCH_2N=CHCO_2Et$) were carried out in acidified DMF, with the addition of varying amounts of water; the results, summarised in Scheme 2, show that the presence of 1-10 mol% of H_2O led to very high yields of the cyclo-adduct. It is likely that the water catalyses the cyclo-addition, but reduces the concentration of the imine by hydrolysis; we hope that careful control of [H_2O] might lead to reliably high yields in many of these aza-Diels-Alder reactions.

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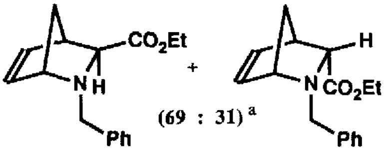
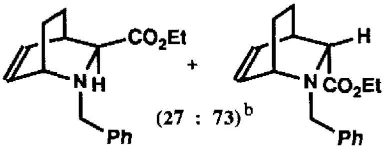
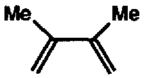
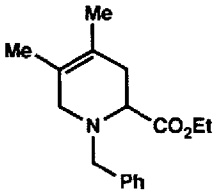
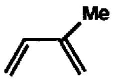
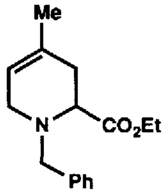
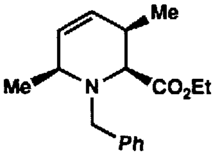
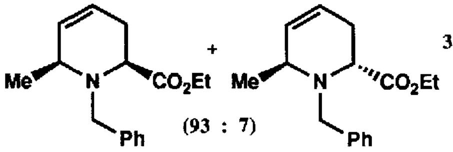
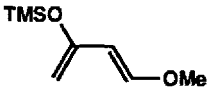
Entry	Diene	Time	Product(s)	Yield[6]
1		15h	 (69 : 31)[a]	89%
2		32h	 (27 : 73)[b]	21%
3		35h		47%
4		35h		43%
5		48h		36%
6		45h	 (93 : 7)	38%
7		45h	No reaction	
8		45h	Diene degraded	

Table. Results from the Diels-Alder reactions of various dienes with the imine derived from $PhCH_2NH_2.HCl$ and $OHC\text{-}CO_2Et$ in DMF.[5] [a] Stereochemistry assigned from NOE experiments and ^{1}H δ correlation[7]. [b] Stereochemistry assigned from ^{1}H NMR W-coupling and δ correlation.[8]

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5. **Method.** In a typical procedure, ethyl glyoxylate (612mg, 6mmol) and benzylamine hydrochloride (612mg, 4.3mmol) were dissolved in DMF (14ml) under argon. To this was added cyclopentadiene (566mg, 8.6mmol), and the mixture was stirred for 15h at room temperature. Standard work-up, followed by flash chromatography, yielded the Diels-Alder adduct.

6. All the adducts are new compounds, and gave satisfactory IR, ^{1}H NMR, ^{13}C NMR, *and high resolution mass spectra.*

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