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AZA DIELS-ALDER REACTIONS IN WATER: CYCLOCONDENSATION OF C-ACYL IMINIUM IONS WITH CYCLOPENTADIENE

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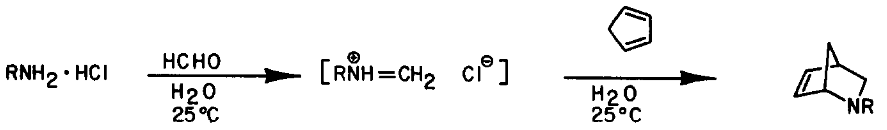
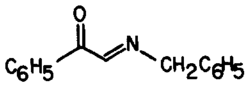
Summary: C-Acyl-N-alkyl iminium ions as well as C-acyl N-unsubstituted iminium ions react with cyclopentadiene in water at ambient temperature giving rise to aza Diels-Alder adducts.

We recently described the cyclocondensation of simple unactivated iminium salts (e.g. methylene iminium chloride and methylmethylene iminium chloride) with dienes in water (cf Equation 1).[1] In general simple imines are unreactive toward dienes. However, Danishefsky has shown[2] that imines undergo condensation with the activated diene, 1-methoxy-3-trimethylsiloxydiene, in the presence of zinc chloride. On the other hand, activated N-aryl glyoxyl imines as well as doubly activated imines react with simple dienes under boron-triflouoride etherate catalysis.[3] In contrast, N-alkyl imines (cf. 1) derived from phenylglyoxal do not react with simple dienes (e.g. cyclopentadiene, 2,3-dimethylbutadiene) under Lewis acid catalysis, heating or high pressure.[3] We detail below the reaction of C-acyl N-alkyl iminium ions (cf. 2) and C-acyl N-unsubstituted iminium ions (cf. 3), derived from ammonia, with cyclopentadiene in water.



(1)



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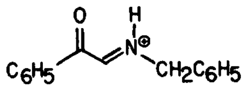

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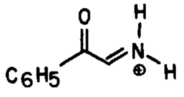

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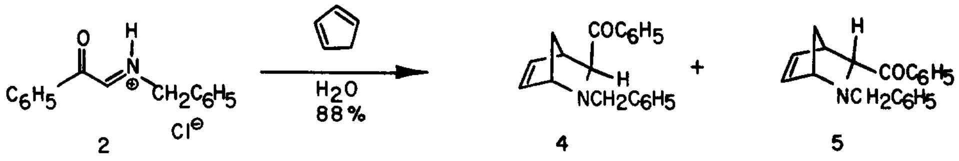
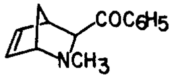
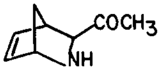
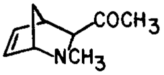
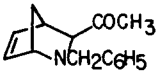
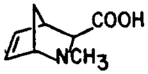
A preliminary experiment focussed on the reaction of cyclopentadiene with iminium ion 2 derived from phenylglyoxal and benzylamine. Addition of neat cyclopentadiene (2.0 equiv) to a 2.0 M solution of benzylamine hydrochloride (1.0 equiv) in water containing 1.2 equivalents of phenylglyoxal afforded a heterogeneous reaction mixture which after 22 h at ambient temperature gave rise to an 88% yield of 4 and 5 in the ratio of 3:2. Use of monomethylamine hydrochloride in the above reaction provided an 82% yield of Diels-Alder adducts (see Table 1, entry 1). Particularly noteworthy is the reaction of 3, generated in situ from a saturated ammonium chloride solution and phenylglyoxal, with cyclopentadiene which proceeds smoothly in 89% yield giving rise to a mixture (endo-exo, 2:1) of Diels-Alder adducts 6 and 7 which were isolated as their hydrochloride salts. Similar reaction of ammonium chloride with pyruvic aldehyde proceeded in 84% overall yield (entry 2). Additional examples employing pyruvic aldehhyde can be found in the Table.



Diels-Alder adducts such as 6 and 7 are readily converted into cyclopentene derivatives. For example, exposure of 6 and 7 to zinc in glacial acetic acid for 45 min afforded after workup a 76% yield of 8, which was isolated as its

Table Reaction of Cyclopentadiene with C-Acyl Iminium Ions[a]

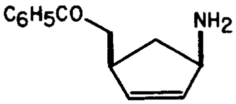
Entry	Substrate	Amine	Time/h	Product(s)[d]	Exo/Endo Ratio	Yield/%[b]
1	C_6H_5COCHO	$CH_3NH_2 \cdot HCl$	22		4.2:1	82
2	CH_3COCHO	NH_4Cl	22		1:2	84[c]
3	CH_3COCHO	$CH_3NH_2 \cdot HCl$	20		3.6:1	67
4	CH_3COCHO	$C_6H_5CH_2NH_2 \cdot HCl$	18		10:1	65
5	HOOCCHO	CH_3NH_2	22		1.9:1	86

[a] All reactions were run in 2.0 M aqueous solution of the amine salt (1.0 equiv) employing 1.2 equiv of substrate and 2.0 equiv of cyclopentadiene.

[b] Isolated yields.

[c] Isolated as hydrochloride salt.

[d] Exo/endo ratios were determined by ^1H NMR.



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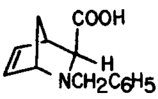
hydrochloride salt. Cyclopentene derivatives such as 8 represent potential precursors to carbocyclic analogs of purine ribo and deoxyribonucleosides.[4]

In a separate series of experiments we examined glyoxylic acid as a potential substrate for the aza Diels-Alder reaction. It was found that a heterogeneous mixture of cyclopentadiene (2.0 equiv) in water containing glyoxylic acid (1.2

equiv) and benzylamine hydrochloride (1.0 equiv) provided after 22 h at ambient temperature an 80% yield of carboxylic acids 9 and 10[5] in a ratio of 1.4:1.



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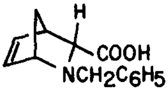

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When employing glyoxylic acid as a substrate, one need not employ an amine hydrochloride salt to promote iminium ion formation. For example, condensation of cyclopentadiene in water with the iminium ion derived from 1.2 equivalents of glyoxylic acid and 1.0 equivalent of monomethylamine provided in 86% yield a mixture of endo and exo acids (see Table).

Work is currently in progress to further expand the scope of the iminium Diels-Alder reaction and to examine its effectiveness in the construction of naturally occurring alkaloids.

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4. Y.F. Shealy and J.D. Clayton, J. Amer. Chem. Soc., 91, 3075 (1969); G. Just and G. Reader, Tetrahedron Letters, 1521 (1973).
5. Compounds 9 and 10 were isolated as their amine hydrochloride salts.

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