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THE REMARKABLE REACTIVITY OF 2-ALKYLIDENE-IMIDAZOLIDINES IN INVERSE DIELS-ALDER REACTIONS

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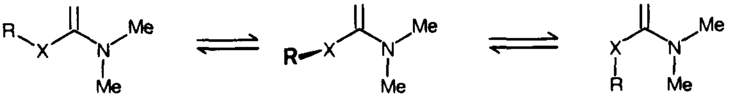
Summary: The reactivity of 2-alkylidene-imidazolidines 2 in inverse Diels-Alder syntheses with several pyridazines and 1,2,4-triazines is compared with that of acyclic ketene acetals 1. The 2-cyclopropylidene-imidazolidine 2c is particularly suited for less reactive dienes.

Extensive work of Sauer[1)] and others[2)] has shown that ketene N,N-acetals 1a are less reactive in inverse electron demand Diels-Alder reactions than N,S- or N,O-acetals 1b or 1c, respectively, contradicting anticipations based on HOMO energies of these dienophiles[1,3)]. This discrepancy might be traced back to steric restraints. Only the N,S- and N,O-acetals 1b and 1c can adopt an all planar conformation A without steric repulsions. For the N,N-acetal 1a the identical conformations A and C are energetically less favourable. Merely in the all planar conformations the reactivity of the ketene acetals 1a - c can be expected to correlate with their HOMO energies[4)], as steric hindrance is of comparable size.

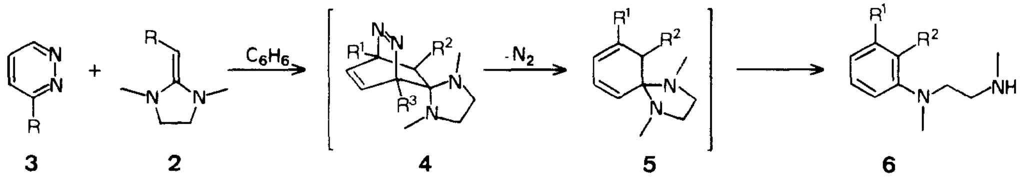


A B C

1	R	X
a	Me	NMe
b	Me	S
c	Et	O

If the substituents R are turned out of the plane of the double bond[5)], attack of the π-system is expected to be impaired from both sides in 1a alone. Thus, the all planar conformation A being preferred and with less steric hindrance in a perpendicular conformation B for 1b and 1c, the reactivity enhancing effect of a high HOMO energy in 1a is more than compensated. If the N,N-acetal is forced into a planar conformation by the constraints of a ring like in the alkylidene-imidazolidines 2, these steric effects should be removed.

Indeed, whereas 1a is known to react only with very electron deficient tetrazines and triazines, which are further activated by at least one carboxylic ester group[2)], 2-methylene-imidazolidine[6)] 2a underwent an inverse Diels-Alder reaction even with unsubstituted pyridazine 3a in benzene at 160°C. 84% of N,N'-dimethyl-N-phenyl-1,2-ethanediamine[7)] 6a were isolated[8)] in this cycloaddition, that probably occurred via the primary cycloadduct 4a, which first lost nitrogen to form the intermediate 5a and then eliminated amine to create the aromatic system, a mechanism generally accepted for this type of reaction[2)]. In a similar way the 3-methylpyridazine 3b led to a mixture of regioisomers, 14% 6b (via 4/5b) and 66% 6c (via 4/5c). The o-tolyl substituted diamine 6b was formed in 89% yield free of the isomer 6c via a different intermediate 4d, when the pyridazine 3a was heated with the 2-ethylidene-imidazolidine[6)] 2b in benzene at 192°C in a sealed tube for 9 h.



2,3	R
a	H
b	Me

4	R^1	R^2	R^3
a	H	H	H
b	H	H	Me
c	Me	H	H
d	H	Me	H

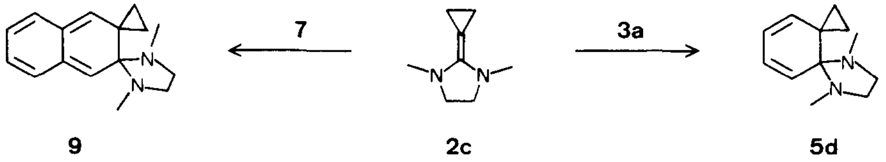
5,6	R^1	R^2
a	H	H
b	H	Me
c	Me	H

The more reactive 2,3-naphthacene 7 cycloadds to 2-methylene-imidazolidine 2a at lower temperatures. After 75 min at 105°C without solvent, 79% of the (2-naphthyl)-ethanediamine 8a were distilled from the reaction mixture. The 3-methyl-2-naphthyl derivative 8b was formed from 2b and 7 in quantitative yield after 1 h at 173°C in benzene.

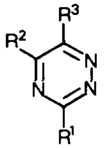
8	R
a	H
b	Me

The reaction rate could be further enhanced by using the strained 2-cyclopropylidene-imidazolidine[6)] 2c as dienophile. 2c reacted vigourously with the pyridazine 3a at room temperature and even faster with the 2,3-naphthacene 7. At

0°C nitrogen evolution was complete within minutes with 3a and within seconds using 7. As there are no α-hydrogen atoms available, aromatization cannot occur and the spiro substituted cyclohexadienes 5e and 9 were formed in 94% and 96% yield, respectively, corroborating the generally accepted mechanism outlined above.



While these inverse Diels-Alder reactions of not activated pyridazines are unique with 2-alkylidene-imidazolidines, ketene N,N-, N,O- and N,S-acetals react smoothly with 1,2,4-triazines2) at temperatures between 20°C and 100°C, thus allowing the direct comparison with the 2-alkylidene-imidazolidines 2. The ketene acetals 1a, 1b and 1c all cycloadd to methyl 1,2,4-triazine-3-carboxylate 10a (R = Me)9) at 40°C. 2a reacted vigourously at 0°C with 10a (R = Et), nitrogen evolution being complete within a few seconds. Even at -20°C in toluene nitrogen evolution was clearly visible10) and ended before the slowly warming reaction mixture had reached 0°C after 1 h, yielding 11a free of regioisomers.



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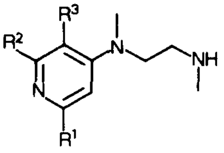
10	R^1	R^2	R^3	11
a	CO_2R	H	H	a
b	H	H	H	
c	H	Ph	H	
d	H	Ph	Ph	b



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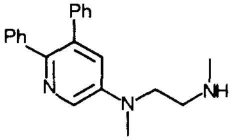

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The unsubstituted 1,2,4-triazine 10b needed reaction temperatures of 100°C in dioxane to form 27% of 4-dimethylaminopyridine11) with 1c in 12 h, the 5-phenyl-1,2,4-triazine 10c lead to a mixture of 58% 4-dimethylamino- and 8% 5-dimethylamino-2-phenylpyridine11) with 1c in refluxing dioxane after 3 - 6 d. The 2-methylene-imidazolidine 2a underwent cycloaddition with the sterically more hindered 5,6-diphenyl-1,2,4-triazine12) 10d at room temperature to form the 4-amino-substituted pyridine 11b. At 79°C 10% of the regioisomer 12 were also identified besides 86% of 11b. With approximately 1 M solutions the reaction was completed >95% within a few hours. The lower reactivity of 5,6-diphenyl-substituted 1,2,4-triazines is documented in the 3-carboxylic ester series, where even 1-diethylamino-propyne adds only at 80°C in benzene9,13).

The only ketene acetals known to react with acyclic dienes in an all carbon (4 + 2)-cycloaddition[14] are the alkylidene-imidazolidines 2. They belong to the most reactive dienophiles for inverse electron demand Diels-Alder reactions, comparable or maybe even surpassing the 1-diethylamino-propyne, which is known to be superior to the acyclic ketene acetals[15] 1a - c. Particularly the cyclopropylidene derivative 2c shows a tendency to form cycloadducts hitherto unknown and should be the reagent of choice for reluctant dienes.

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