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PREPARATION OF DI- AND TRIACYLIMINES AND THEIR USE IN THE SYNTHESIS OF NITROGEN HETEROCYCLES

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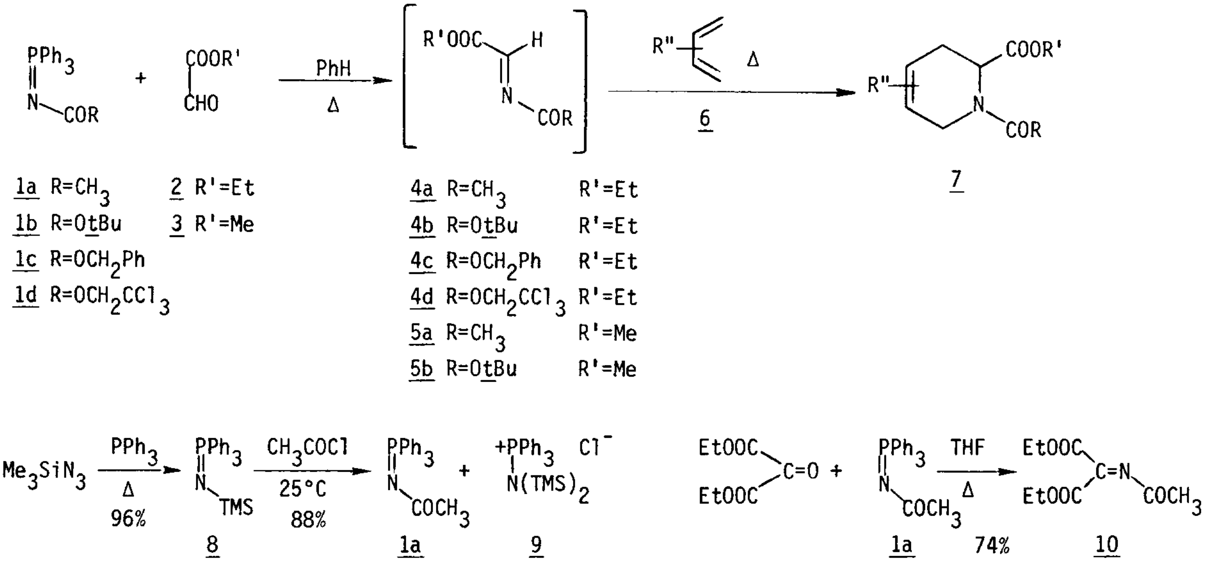
Abstract: Reaction of aza-Wittig reagents with glyoxylates and keto malonates produces di- and tri acylimines which are moderately reactive dienophiles for Diels-Alder cycloaddition.

In the last few years, a considerable amount of synthetic effort has been expended on demonstrating the utility of the imino Diels-Alder reaction.[2] In the course of work directed toward the tota synthesis of pyrrolizidine and indolizidine alkaloids, we have investigated the synthesis of di- an triacylimines and their reactivity as Diels-Alder dienophiles.

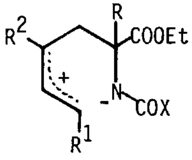
The diacylimines 4a-d and 5ab were prepared (Scheme) by an aza-Wittig reaction between the phosphineimines 1a-d and the glyoxylates 2 or 3.[3] These diacylimines were not isolated but rather reacted in situ with various dienes 6 to give fair to good yields of the corresponding cycloadducts 7 The N-acetylphosphineimine 1a has been reported previously from the reaction of iminotriphenylphosphorane and acetyl chloride.[4] However, to avoid the use of the readily hydrolyzable N-unsubstitute compound,[5] the preparation of 1a from N-trimethylsilyliminotriphenylphosphorane 8 was effected. Reaction of trimethylsilyl azide with triphenylphosphine afforded a 96% yield of 8[6] which was reacted with acetyl chloride to produce 1a and 9 in 88% yield. The N-carboalkoxyiminotriphenylphosphoranes 1b-d were all prepared from the corresponding azides.[7] The triacylimine 10, prepared by a similar approach from the aza-Wittig reagent 1a and diethyl oxomalonate[8] in 74% yield, could be isolated as stable oil (bp 105-110°C, 0.25 Torr).

The Diels-Alder reactions were generally carried out in refluxing benzene or dimethoxyethane (DM for 15 hours. The results of these cycloadditions are shown in the Table. Several observations should be made. The di- and triacylimines - 4, 5, and 10 - are moderately active dienophiles, givi good yields of adducts only with activated dienes [e.g., Danishefsky's diene 6a,[9a] Cohen's diene 6b,[9b] and cyclopentadiene 6e. With less reactive dienes, e.g., 6c[9c] and 6d[9d] the yields are only fair. It is to be noted that all of these cycloadditions are carried out under one atmosphere of pressure and did not require the high pressure conditions described by Plieninger.[3] Reaction of th imine 4b with unsymmetrical dienes having a substituent in the 1-position, i.e., 6a and 6b, proceed regiospecifically with the substituent ending up α to the nitrogen atom in the product, i.e., 7a an 7b. This is in agreement with the generalization of Weinreb[2b] concerning the regiochemistry of imin Diels-Alder reactions. Thus one would expect the major product to be produced via the more stable



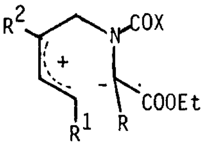
Scheme

polar transition state (or intermediate) A, in which the negative charge rests on the activated nitrogen atom, rather than B. When the R group is an ester (so that the anion of B is an α-acetamido malonate), namely in the triacylimine reaction (example 9), the energy difference is less and a 3:1 mixture of products, 7i and 7j, is formed with that resulting from A, 7i, being predominant.



A

vs

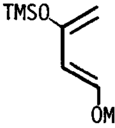
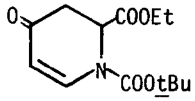
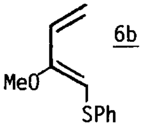
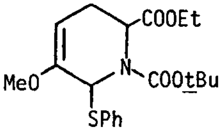
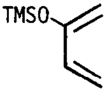
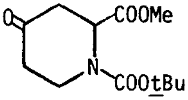
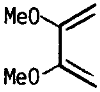
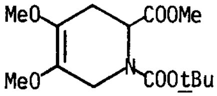
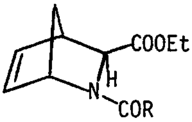
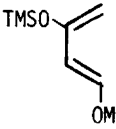
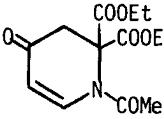
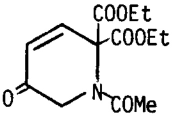


B

Chromatography of the mixture resulting from the reaction of 5b with 6c followed by methanolysis afforded a fair yield of the 4-piperidinone 7c as the major product. We were unable to identify any of the corresponding regioisomer, the 3-piperidinone, among the minor byproducts, although we can not conclusively rule out its presence.

The structures of the adducts were inferred from their NMR, IR, and mass spectral data. For example, the ^{1}H NMR of the piperinone 7a exhibited two doublets (J = 8 Hz) for the vinylogous amide protons at δ 7.85 and δ 5.30, thus implying that the cycloaddition had occurred with the assigned regiochemistry. The structure of 7c was verified by comparison with an authentic sample prepared in 93% yield by catalytic hydrogenation of the methyl ester corresponding to 7a (cycloaddition of 5a and 6a, 56%). The 200 MHz NMR spectrum of 7e at 30°C exhibited two sets of peaks for each set of protons in the molecule. However, when the spectrum was taken at 100°C, each pair of peaks coalesced, thus indicating isomerism about the C-N amide linkage and not an *endo-exo* mixture. The *exo* stereochemistry of the ethyl ester was inferred from the fact that the proton α to the ester occurs as a clean singlet and thus should occupy the *endo* position. This result is not surprising for the following reasons. First, the two large groups should be *trans* in the dienophile 4a. Second, since the

TABLE: Diels-Alder Reactions of Di- and Triacylimines

Example	Imine	Diene	Adduct	Yield(%)	Conditions
(1)	EtOOCCH=NCOOtBu 4b	 6a	7a 	84	1) PhH/Δ/15h 2) H_3O+
(2)	EtOOCCH=NCOOtBu 4b	 6b	7b 	56	PhH/Δ/12h
(3)	MeOOCCH=NCOOtBu 5b	 6c	7c 	30	1) PhH/Δ/15h 2) MeOH/K_2CO_3
(4)	MeOOCCH=NCOOtBu 5b	 6d	7d 	16	PhH/Δ/15h
	EtOOCCH=NCOR				
(5)	4a R = Me	6e	7e R = Me	81	DME/Δ/15h
(6)	4b R = OtBu		7f R = OtBu	55	
(7)	4c R = OCH_2Ph		7g R = OCH_2Ph	57	
(8)	4d R = OCH_2CCl_3		7h R = OCH_2CCl_3	61	
(9)	$(EtOOC)_2C$=NCOMe 10	 6a	 +  7i 7j	45:15	1) 140°C/2h 2) H_3O+

nitrogen dominates the orientational preference, the carbonyl group on nitrogen should be endo in the preferred transition state. Thus one would expect the formation of the adduct with the carbonyl group on nitrogen initially endo and the ethyl ester exo.

Finally, as a model for a Diels-Alder approach to glycosides,[10] a mixture of 3 and 6a in benzene was refluxed for 15h and then treated with 0.1N HCl in aqueous THF for 1h to produce in 71% yield an approximately 1:1 mixture of stereoisomers of 11.

The tetrahydropyridines and bicyclic amides produced by this methodology are potential intermediates for the construction of a variety of alkaloids. Further investigations along these lines are currently underway.

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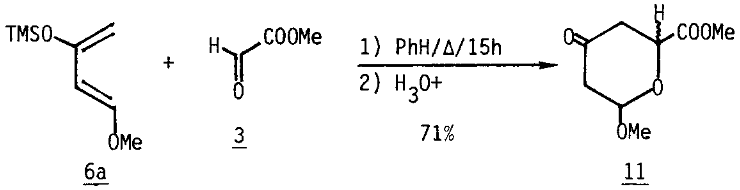

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1. Camille and Henry Dreyfus Teacher-Scholar, 1978-83; Alfred P. Sloan Foundation Fellow, 1979-81.
2. a) Most of the recent work has been accomplished in the groups of Weinreb, Krow, Moore, and others. b) For an excellent review and leading references, see: S. M. Weinreb and J. I. Levin, *Heterocycles*, **12**, 949 (1979).
3. For examples of this type of construction of acylimines see: a) H. Plieninger and D. vor der Brück, *Tetrahedron Lett.*, 4371 (1968); b) D. vor der Brück, R. Bühler, and H. Plieninger, *Tetrahedron*, **28**, 791 (1972).
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7. H. R. Kricheldorf, *Synthesis*, 695 (1972) reported the preparation of 1b by this route. The iminophosphorane 1c was synthesized by a different route [A. J. G. Baxter and A. B. Holmes, *J. Chem. Soc. Perkin Trans. I*, 2343 (1977)] while compound 1d has not been prepared before.
8. It was found that diethyl oxomalonate could be obtained quite easily in good yield (62%) from ozonolysis of the readily available diethyl ethylidenemalonate in CH_2Cl_2 followed by reductive workup with triphenylphosphine and distillation from phosphorus pentoxide. This method is preferable to the direct oxidation of diethyl malonate. A. W. Dox, *Org. Syn. Coll. Vol. I*, 266 (1932).
9. The dienes were prepared by known methods as follows: a) 1-methoxy-3-trimethylsilyloxy-1,3-butadiene: S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974); b) 2-methoxy-1-phenythio-1,3-butadiene: T. Cohen, R. J. Ruffner, D. W. Shull, E. R. Fogel, and J. R. Falck, *Org. Synth.*, **59**, 202 (1979); c) 2-trimethylsilyloxy-1,3-butadiene: M. E. Jung and C. A. McCombs, *ibid.*, **58**, 163 (1978); d) 2,3-dimethoxy-1,3-butadiene: E. McDonald, A. Suksamrarn, and R. D. Wylie, *J. Chem. Soc. Perkin Trans. I*, 1893 (1979).
10. For other similar approaches, see: a) S. David, *et al.*, *J. Chem. Soc. Perkin Trans. I*, 1795 (1979); 2274 (1974); *Chem. Commun.*, 535 (1978); *Tetrahedron*, **34**, 299 (1978) and references therein. b) J. Jurczak, *et al.*, *J. Org. Chem.*, **44**, 3347 (1979) and references therein.

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