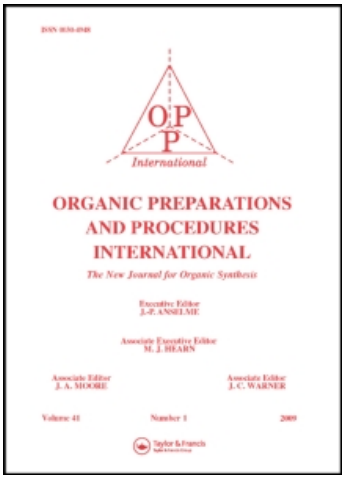

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A NOVEL SYNTHESIS OF 2-ACYLPYRIDINES *via* INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF 5-ACYL-1,2,4-TRIAZLNES

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OPPI BRIEFS

A NOVEL SYNTHESIS OF 2-ACYLPYRIDINES *via* INVERSE ELECTRON DEMAND DIELS-ALDER REACTION OF 5-ACYL-1,2,4-TRIAZINES †

Submitted by (04/12/01)

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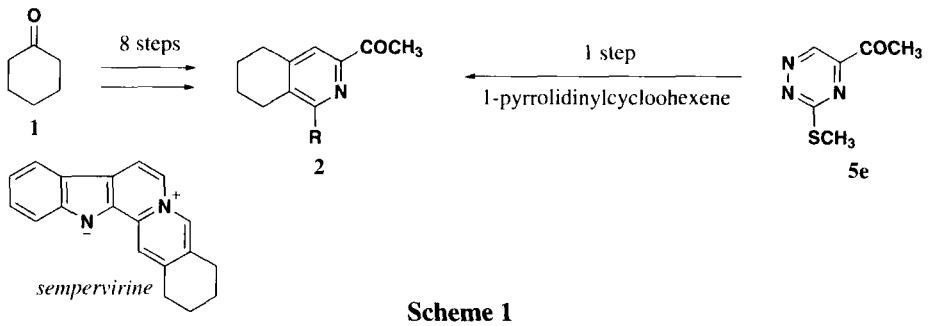
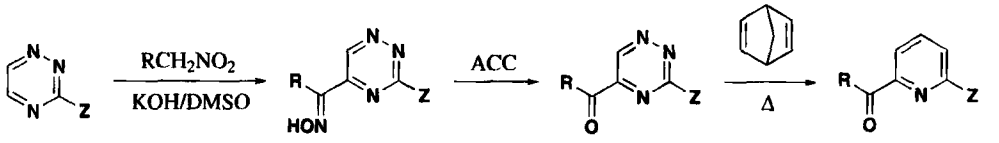
Inverse electron-demand Diels-Alder reactions of heteroaromatic systems possessing a suitable azadiene arrangement are currently of great practical use for the synthesis of heterocycles.[1] 1,2,4-Triazines can react in several ways as Diels-Alder azadienes with electron-rich dienophiles to give addition products, which subsequently generate other heterocyclic systems in a retro Diels-Alder reaction step.[2] Such reactions provide access to novel pyridines or pyrimidines and have been employed, *inter alia*, in the total synthesis of natural products[3], biologically active compounds[4] or ligands for coordination chemistry.[5] In the context of our interest in zwitterionic indole alkaloids, we required a convenient synthesis of 3-acetyl-5,6,7,8-tetrahydroisoquinoline (**2**) (R = H) for the preparation of *sempervirine*.[6] This compound has previously been obtained in an eight-step synthesis starting from cyclohexanone (**1**); however the overall yield of **2** is very low.[7] Using the Diels-Alder annulation methodology, we were able to prepare the thiomethyl derivative of **2** (R = SCH_3) from 5-acyl-3-methylsulfanyl-1,2,4-triazine **5e** and 1-pyrrolidinylcyclohexene in 81% yield and applied it for the formal synthesis of *sempervirine* (*Scheme 1*).[6] This paper describes a further development based on our previous work using norbornadiene instead of an enamine as the dienophile; it allows us to elaborate a more general route to monocyclic 2-acylpyridines **6a-h**.



Scheme 1

Although a variety of methods have been used for the syntheses of pyridylketones,[8,9] a straightforward preparation from 5-acyl-1,2,4-triazines using the Diels-Alder methodology, has not been reported. The key intermediates are the 5-acyl-1,2,4-triazines (**5a-h**) carrying different alkyl substituents at the carbonyl carbon. They have been prepared from 1,2,4-triazines (**3a-c**) *via* regioselective nucleophilic acylation with alkyl nitronate ions at position 5, leading to the oximes of 5-acyl-1,2,4-triazines (**4a-h**)[6,10,11] which were subsequently cleaved to the corresponding 1,2,4-triazin-5-yl ketones (**5a-h**) with ammonium chlorochromate (ACC) absorbed on aluminium oxide,[12] in chloroform at room temperature (*Scheme* 2). The method described here is more efficient than the one previously reported,[6] which involves the use of sodium hydrosulfite in aqueous dioxane (Table 1).

The conversion of the 5-acyl-1,2,4-triazines (**5a-h**) into the corresponding 2-acylpyridines (**6a-h**) is outlined in Scheme 2. Although acetylene itself has apparently not been used as a dienophile in reaction with 1,2,4-triazines, its equivalent, norbornadiene, has found several applications.[2] Heating



Scheme 2

5-acyl-1,2,4-triazines (**5a-h**) with norbornadiene in boiling *p*-cymene for 5 hours gives the corresponding 2-acylpyridines (**6a-h**) in good yields (Table 2). The structures of **6a-h** were assigned based on their spectroscopic properties and microanalyses. Their IR spectra displayed the characteristic C=O streching vibrations at 1695-1702 cm^{-1}. Their ^1H NMR spectra showed chemical shifts and coupling constants characteristic for three neighboring protons of the pyridine ring, in addition to the signals for the aliphatic and aromatic protons (Table 2).

Table 1. Comparison of Selective Cleavage of Oximes of 5-Acyl-1,2,4-triazines **4** with Ammonium Chlorochromate (ACC) and Sodium Hydrosulfite

Cmpd[a]	Z	R	Yield (%)	
			ACC	$Na_2S_2O_4$
5a	C_6H_5	CH_3	83	71[b]
5b	C_6H_5	C_2H_5	82	68[b]
5c	C_6H_5	C_3H_7	92	79[b]
5d	C_6H_5	C_4H_9	87	71[b]
5e	SCH_3	CH_3	77	64[c]
5f	SCH_3	C_2H_5	90	65[d]
5g	$SCH(CH_3)_2$	CH_3	98	52[d]
5h	$SCH(CH_3)_2$	C_2H_5	95	90[d]

a) All products are known compounds and their physical constants, IR and ^1H NMR spectra correspond to those reported in literature. b) Ref. No. 12. c) Ref. No. 7. d) Ref. No. 11.

Table 2. Yields, m.p., Elemental Analyses and ^{1}H NMR Data for 2-Acylpyridines

Cmpd	Yield (%)	mp. (^{0}C)	Elemental Analysis (Found) C	H	N	^{1}H NMR (δ)
6a	82	76.5-77	79.19 (79.29)	5.58 (5.58)	7.11 (7.12)	2.83(s, 3H), 7.45-7,57(m, 3H), 7.89-8.01(m, 3H), 8.08-8.11(m, 2H)
6b	63	67-68	79.62 (79.41)	6.16 (6.35)	6.63 (6.61)	1.26(t, 3H, *J*=7.26 Hz), 3.38(q, 2H *J*=7,31 Hz), 7.45-7.57(m, 3H), 7.87-8.01(m, 3H), 8.08-8.14(m, 2H)
6c	73	39-40	80.00 (79.82)	6.67 (6.69)	6.22 (6.18)	1.04(t, 3H, *J*=7.19 Hz), 1.82(sekstet, 2H, *J*=7.43Hz), 3.32(t, 2H, *J*=7.19 Hz), 7.45-7.58(m, 3H), 7.87-8.00(m, 3H), 8.08-8.14(m, 2H)
6d	92	45.5-46	80.33 (80.11)	7.11 (7.17)	5.86 (5.75)	0.98(t, 3H, *J*=7.24 Hz), 1.35-1.60(m, 2H), 3.34(t, 2H, *J*=7.22 Hz), 7.45-7.65(m, 3H), 7.86-8.00(m, 3H), 8.07-8.14(m, 2H)
6e	73	36-37	57.49 (57.68)	5.39 (5.45)	8.38 (8.09)	2.63(s, 3H), 2.72(s, 3H) 7.35(dd, 1H, J_1= 1.17 Hz, J_2=7.83 Hz), 7.61 (t, 1H, *J*=7.79 Hz), 7.70(dd, 1H, J_1=1.21 Hz, J_2=7.53 Hz)
6f	42	36.5-37	59.67 (59.48)	6.08 (5.87)	7.73 (7.74)	1.21(t, 3H, *J*=7.26 Hz), 2.62(s, 3H), 3.24(k, 2H, J_1=7.05 Hz), 7.34(d, 1H, *J*=7.85 Hz), 7.61 (t, 1H, *J*=7.69 Hz), 7.70(d, 1H, *J*=7.36 Hz)
6g	75	oil	51.20 (51.09)	4.53 (4.56)	18.67 (18.86)[a]	1.44(s,3H), 1.48(s,3H), 2.70(s,3H), 4.08(septet, 1H, *J*=6.81 Hz), 7.28(dd, 1H, J_1=1.23 Hz, J_2=7.83 Hz), 7.70(dd, 1H, J_1= 1.23 Hz, J_2=7.57 Hz)
6h	74	oil	52.44 (52.32)	4.88 (4.81)	17.99 (17.85)[b]	1.21(t, 3H, *J*=7.26 Hz), 1.44(s, 3H), 1.47(s, 3H), 3.21(k, 2H, *J*=7.32Hz), 4.07(septet, 1H, *J*=6.86 Hz), 7.28(dd,1H, J_1=1.16 Hz, J_2=7.78 Hz), 7.59(t, 1H, *J*=7.71 Hz), 7.69(dd, 1H, J_1=1.21 Hz, J_2=7.55 Hz)

a) 2,4-Dinitrophenylhydrazone of 2-acetyl-6-isopropylthiopyridine (**6g**), mp. 196°.
b) 2,4-Dinitrophenylhydrazone of 2-propanoil-6-isopropylthiopyridine (**6h**), mp. 149°.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were measured with a Magna IR-760 spectrophotometer in KBr pellets. The ^{1}H NMR spectra were recorded in deuteriochloroform on a Varian-Gemini 200 Hz spectrometer.

Preparation of 5-Acyl-1,2,4-triazines (5a-h). General Procedure.- To a solution of compounds **4a-h** (1 mmol) in chloroform (30 mL), ammonium chlorochromate absorbed aluminum oxide (1.5 g, 2 mmol) was added, and the resulting mixture was stirred for 24 hours at room temperature. After that time the solid was filtered off. The filtrate was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, chloroform). The yields of compounds **5a-h** are outlined in Table 1.

Preparation of 2-Acylpyridines (6a-h). General Procedure.- To a solution of the corresponding 5-acyl-1,2,4-triazine (**5a-h**) (1 mmol) in *p*-cymene (5 mL) was added norbornadiene (1.1 mL, 10 mmoles). The reaction mixture was refluxed for 5 hrs. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane:chloroform 2:5). The crude product was recrystallized from ethanol-water mixture to give **6a-f**. Compounds **6g-h** were obtained as the corresponding 2,4-dinitrophenylhydrazones. For analytical and spectroscopic data see Table 2.

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SYNTHESIS OF HAPTEN PHOSPHORAMIDITES

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(3/29/01)

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Oligonucleotide probes containing non-radioactive hapten reporter groups are used in amplified nucleic acid testing (NAT) assays that identify sequences of clinical interest in patient samples.[1,2] Structurally diverse haptens and other reporter groups have been efficiently introduced into oligonucleotide probes on automated synthesizers using phosphoramidite chemistry.[3,4] In 1996, we described the synthesis of phosphoramidite probes containing haptens such as adamantane, carbazole and dansyl, in a 1,3-diol framework.[5] These bifunctional reagents were suitable for incorporation at either the 3′ or 5′ end of the oligonucleotide or within the sequence. This flexibility is extraneous if 5′ labeling is all that is required. This paper describes the synthesis of monofunctional phosphoramidites based on the same haptens (adamantane **5a,b**, carbazole **9a,b**, dansyl **12a,b**) but designed exclusively for 5′ labeling. Phosphoramidites with both C-6 aliphatic and solubility-enhancing oxygenated tethers are reported.

Thus, 2-[3-(4-nitrophenyl)-1-adamantyl]acetic acid (**1**) was coupled with 6-amino-1-hexanol (**2a**) or 2-[(2-aminoethoxy)ethoxy]ethanol (**2b**)[6-8] using HOBt and EDAC in dichloromethane to afford **3a** and **3b** in 80 and 81% yield respectively (*Scheme 1*). The hydroxyl group in **3a** and **3b** was then converted to the 2-(cyanoethyl)-*N,N*-diisopropylphosphoramidite functionality by treatment with (2-cyanoethyl)-*N,N*-diisopropylchlorophosphoramidite (**4**) and *N,N*-diisopropylethylamine (DIEA) to afford the phosphoramidites **5a** and **5b** in 41 and 61% yield, respectively.