

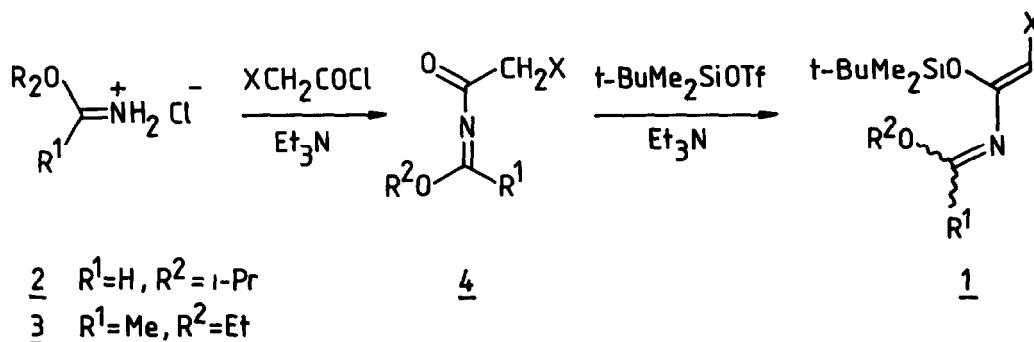
A DIELS-ALDER ROUTE TOWARDS PYRIMIDIN-4-ONES

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Abstract N-acylimidates 4 are readily silylated with t-butyltrimethylsilyl triflate in the presence of triethylamine to give 2-aza-1,3-dienes 1. These react with activated nitriles to yield pyrimidin-4-ones 6.

Azadienes are useful reagents for the synthesis of pyridines and piperidines with a defined substitution pattern^{1,2}. We now report a convergent and practical method of synthesis of activated 2-aza-1,3-dienes 1 and their cycloaddition to nitriles bearing electron-withdrawing groups.



Scheme 1

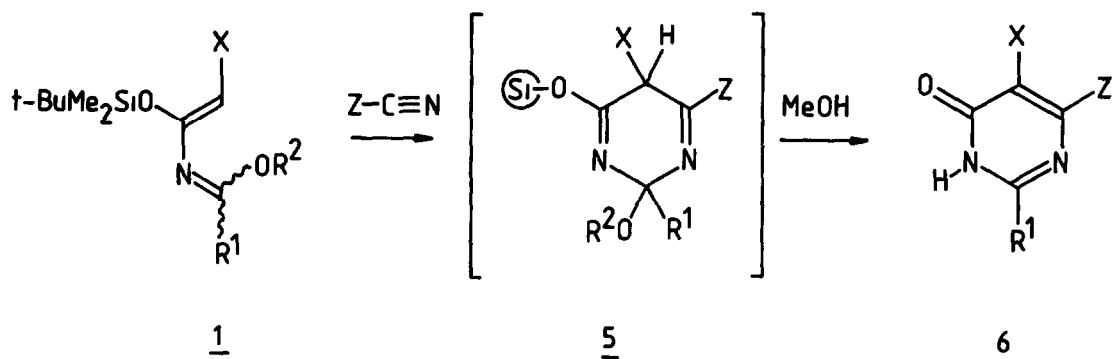
The readily available³ iminoether hydrochlorides 2 and 3 were converted into the corresponding N-acylimidates 4 (Scheme 1, Table 1)⁴. When R¹=H, the more stable i-propoxy derivative 2 was found to give much better results than the corresponding methoxy- or ethoxy derivatives.

N-acylimidates 4 were conveniently silylated with t-butyltrimethylsilyl triflate⁵ in the presence of triethylamine. Carefully purified starting materials 4 yielded after distillation very clean 2-aza-1,3-dienes 1 which could be kept for several months at -20°C (Table 1).

Table 1 Synthesis of 2-aza-1,3-dienes 1⁶

	R ¹	R ²	X	Yield of <u>4</u> [%]	Yield of <u>1</u> [%]
<u>a</u>	H	i-Pr	H	75	77
<u>b</u>	H	i-Pr	Me	70	74
<u>c</u>	H	i-Pr	n-Bu	80	70
<u>d</u>	H	i-Pr	F	73	79*
<u>e</u>	H	i-Pr	Cl	63	69
<u>f</u>	Me	Et	H	90	91

* Mixture of Z and E isomers.



Scheme 2

Table 2 Synthesis of pyrimidin-4-ones 6⁹

	R ¹	X	Z	Conditions	Yield of <u>6</u> [%]
<u>a</u>	H	H	CCl ₃	pure phase, 84°C, 15 min.	90%
<u>b</u>	H	H	Tos	benzene, 20°C, 30 min.	93%
<u>c</u>	H	Me	CCl ₃	pure phase, 84°C, 3 hrs	84%
<u>d</u>	H	Me	Tos	benzene, 50°C, 30 min.	70%
<u>e</u>	H	n-Bu	Tos	benzene, 50°C, 1 hr	60%
<u>f</u>	H	F	Tos	benzene, 50°C, 1 hr	59%
<u>g</u>	H	Cl	Tos	benzene, 50°C, 1 hr	51%
<u>h</u>	Me	H	CCl ₃	pure phase, 84°C, 3 hrs	73%
<u>i</u>	Me	H	Tos	benzene, 50°C, 30 min.	76%

Dienes 1 readily reacted with tosylcyanide^{7,8} or trichloroacetonitrile⁸ to yield cycloadducts 5 which, after aromatization and desilylation gave substituted pyrimidin-4-ones 6 (Scheme 2, Table 2).

Representative Procedures

1) N-acylimidate 4a

Triethylamine (47 ml, 0.356 mole) was added to a vigorously stirred slurry of iminoether hydrochloride 2 (20 g, 0.162 mole) in 350 ml of dry CH₂Cl₂ at - 35 °C. Then 11.5 ml (0.162 mole) of freshly distilled acetyl chloride were rapidly added. Petroleum ether (400 ml, b.p. 40-65°C) was added in one portion to the reaction mixture and the cooling bath was removed. The mixture was filtered off and the filtrate was concentrated in vacuo. The residue was again dissolved in petroleum ether and any insoluble material removed by filtration. The solution was concentrated and the resulting yellow oil was distilled through a 10 cm Vigreux column (bp ~ 55°C/12mm). Yield 15.7 g (75%).

2) 2-aza-1,3 diene 1a

A mixture of 3.5 g (0.027 mole) of 4a and 3.1 g (0.03 mole) of dry triethylamine in 40 ml of dry ether was treated with 7.19 g (0.027 mole) of t-butyltrimethylsilyl triflate diluted in 10 ml of ether. Two phases were observed. The upper ethereal phase was removed and the lower phase washed twice with 2x20 ml of ether. The combined ethereal fractions were concentrated in vacuo and distilled through a 10 cm Vigreux column (bp 67-68°C/0.4 mm). Yield 5.05 g (77%).

3) Cycloaddition of 1a with tosyl cyanide

A solution of 1.3 g (5.35 mmol) of 1a and 0.968 g (5.35 mmol) of tosyl cyanide in 10 ml of benzene was stirred at room temperature for 30 min. The mixture was then treated with 5 ml of methanol. A white solid appeared. After removal of the solvents in vacuo, the residue was suspended in ether, filtered off, washed with ether and dried. The crude cycloadduct 6b was recrystallised in acetonitrile. Yield 1.23 g (93%), mp 280°C (dec).

Acknowledgements

This work was supported by I.R.S.I.A. (Fellowship to Ph.B.), F.N.R.S (fellowship to R.B.) and S.P.P.S. (Action Concertée 86/91-84).

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(Received in France 7 June 1988)