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Acyl Nitronates in Organic Synthesis. An Expeditious Synthesis of 2,5-Dialkylpyrrolidines and 2,5-Dialkylpyrrolines Including Ant Venom Alkaloids

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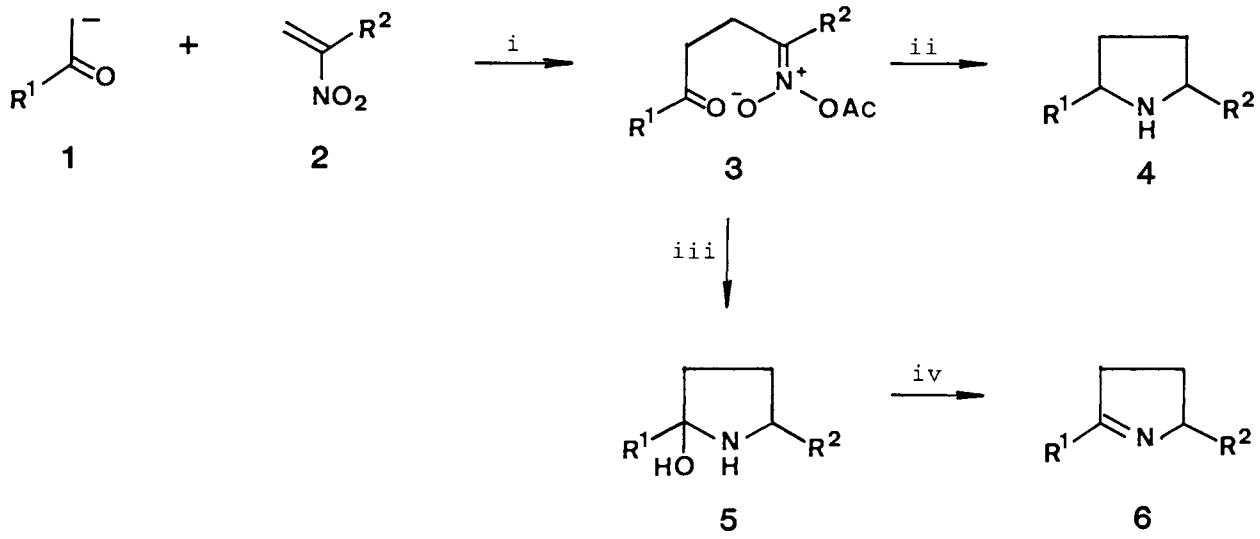
Acetyl nitronates (acetic nitronic anhydrides), readily obtainable from ketones and nitroalkenes, have been demonstrated to serve as potentially useful intermediates for the synthesis of 2,5-dialkylpyrrolidines and 2,5-dialkylpyrrolines, and a short-step synthesis of some ant venom alkaloids has been accomplished via these acetyl nitronates.

Aliphatic nitro compounds have extensively been used in organic synthesis because they serve as versatile synthetic intermediates and a variety of nitro-free compounds as well as nitrogen-containing derivatives are obtainable from these intermediates.[1] In spite of their synthetic potential, however, nitronate esters have found little use in organic synthesis[2] except thermally stable silyl nitronates,[3] and particularly acyl nitronates (acyl nitronic anhydrides) have not been reported so far as useful intermediates.

Recently we reported the facile and high yield preparation of various acetyl nitronates and demonstrated that they serve as promising intermediates for the synthesis of alkylpyrroles,[4] 1,4-diketones,[5] oximes,[5] and pyrrolidines.[5]

There has recently been a resurgence of interest in the synthesis of 2,5-dialkylpyrrolidines which have been identified as characteristic constituents of fire ant venoms.[6] We report herein a short-step synthesis of unsymmetrical 2,5-dialkylpyrrolidines and 2,5-dialkylpyrrolines including ant venom alkaloids via acetyl nitronates.

Hydrogenation of acetyl nitronates **3**, readily prepared from ketone enolates **1** and nitroalkenes **2** as recently reported,[4] was found to give, interestingly, different results depending on a catalyst employed. Thus hydrogenation of **3** over 5% Rh on Al_2O_3 in MeOH (4.5 kg cm^{-2}, 42 h) directly produced 2,5-dialkylpyrrolidines **4**, while hydrogenation over PtO_2 in acetic acid (4.5 kg cm^{-2}, 2-5 h) yielded 2,5-dialkyl-2-hydroxypyrrolidines **5** in good yields (Table 1). Taking into account that various 2,5-dialkylpyrrolidines **4** are accessible from ketones **1** and nitroalkenes **2** in the two steps, the yields of **4** are acceptable. The stereochemistry of **4** was examined by the method of Hill and Chan,[7] i.e., nmr analysis of the corresponding N-benzyl derivatives, and it was found that each pyrrolidine **4** was a mixture of cis and trans isomers in which the former predominated (Table 1).[8]



Scheme 1. Reagents and conditions: i, LDA, THF, -78 °C, then Ac_2O, -78 to 20 °C; ii, H_2 (4.5 kg cm^{-2}), 5% Rh on Al_2O_3, MeOH; iii, H_2 (4.5 kg cm^{-2}), PtO_2, AcOH; iv, PPTS, $CHCl_3$, 60 °C.

On the other hand, the hydroxy pyrrolidines **5** were all crystalline and seemed to be single compounds although their stereostructures were not determined.[9] These unsymmetrical 2,5-dialkylpyrrolidines are important in connection with ant

venom alkaloids, for example trans isomers of **4a**, **c**, and **d** have been isolated from the venom of fire ants, Solenopsis species.[10] In addition, hydroxypyrrolidines **5**

Table 1. Yields (%) of **4**, **5**, and **6**

	Acetylnitronate **3**[a]	**4**	(cis/trans)	**5**[b]	mp/°C	**6**
a	$R^1 = CH_3(CH_2)_4$, R^2 = Bu	34	(86/14)	62	d)	87
b	$R^1 = CH_3(CH_2)_6$, R^2 = Me	53	(82/18)	61(14)[c]	d)	88
c	$R^1 = CH_3(CH_2)_6$, R^2 = Et	53	(83/17)	57	34-35	93
d	$R^1 = CH_3(CH_2)_6$, R^2 = Bu	40	(85/15)	68	39-41	96

a) All acetyl nitronates **3** were prepared in 81-87% yields.

b) Hydrogenation was carried out for 5 h except **3c** which required 2 h.

c) Value in parenthesis is the yield of **4b** accompanied.

d) Crystals of low melting point.

are suitable precursors for the synthesis of another ant venomous constituent, i.e., 2,5-dialkylpyrrolines **6**.[10] Indeed, conversion of **5** to **6** was easily performed by treatment of the former with PPTS[11] (1 equiv.) in $CHCl_3$ at 60 °C (2 h) to give excellent yields of the latter (Table 1). It should be noted that a variety of unsymmetrical pyrrolines **6** can be synthesized efficiently and regioselectively via the acetyl nitronates **3**. Among these products, **6a**, **c**, and **d** have been isolated as ant venomous constituents from the genera Solenopsis and Monomorium.[10] On the other hand, these unsymmetrical 2,5-dialkylpyrrolines **6** have been known to give trans-pyrrolidines **4** predominantly by metal hydride reductions.[6a]

Since a variety of acetyl nitronates **3** are readily available by a combination of ketones **1** and nitroalkenes **2**, the present method provides a facile entry to alkylpyrrolidines and pyrrolines as well as polyalkylpyrroles.[4] Further extension of the utility of acyl nitronates are under way in this laboratory.

References

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8) Since the signals of the respective N-benzyl protons of the cis and trans isomers, a singlet and an AB quartet in $CDCl_3$, respectively, overlapped each other, the ratio was determined by the signals of methine protons adjacent to the nitrogen atom; the methine protons of the cis isomers appeared in the higher field (ca. 0.3-0.6 ppm) than those of the trans isomers.

9) The stereochemistry of two alkyl substituents in 5 is probably trans since the pyrrolidine ring of 5 is presumably formed by the thermodynamically more stable conformation.

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