

Convenient and General Synthesis of Polyalkylpyrroles from Ketones and Nitroalkenes

Masaaki Miyashita, Bahlul Z. Elshaiwi Awen, and Akira Yoshikoshi*

Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan

A convenient and general method has been developed for the synthesis of polyalkylpyrroles starting from ketones and nitroalkenes *via* reduction of the intermediate acetic nitronic anhydrides.

The synthesis of pyrroles gains its importance since these heterocycles are the dominant sub-units in the pigments of life.¹ The pyrrole synthesis most often used today is the Knorr reaction,² which gives satisfactory results when the second component is a β -keto-ester or a β -diketone resulting in formation of a pyrrolecarboxylate or an acylpyrrole, respectively. Usually, however, simple aliphatic ketones cannot be used successfully in the Knorr reaction so that *C*-alkylpyrroles have to be derived from the resulting pyrrolecarboxylates or acylpyrroles,² although a few procedures for the direct synthesis of 3,4-di-alkylpyrroles³ or *N*-acyl-alkylpyrroles⁴ have recently been reported.

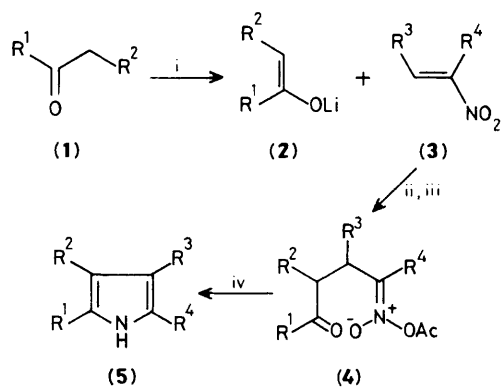
We report here a convenient and general method for the synthesis of polyalkylpyrroles starting from ketones (**1**) and nitro-alkenes (**3**).⁵

A ketone enolate (**2**), generated with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF), reacts with a variety of conjugated nitroalkenes (**3**) to yield the Michael adducts, lithium nitronates,⁶ which are trapped with acetic anhydride to give the corresponding acetic nitronic anhydrides (**4**) as a stereoisomeric mixture in excellent yields (Scheme 1). As shown in Table 1, various acetic nitronic anhydrides are readily obtainable in high yields.⁷ These anhydrides (**4**) are stable in marked contrast to the lability of alkyl nitronates[†] and can be purified by silica gel column chromatography.

[†] Alkyl nitronates (nitronic esters) have been known to decompose easily on standing to form oximes and aldehydes or ketones, whereas silyl nitronates are thermally stable. For reviews, see refs. 7 (pp. 417–459) and 6a.

Table 1. Synthesis of alkylpyrroles from ketones and nitroalkenes.

Entry	Ketone	Nitroalkene	Acetic nitronic anhydride, yield/%	Pyrrole	Yield from anhydride/%
1	(1a)	(3a)	81	(5a)	65
2		(3b)	91	(5b)	64
3		(3c)	74	(5c)	68
4	(1d)	(3a)	87	(5d)	67
5		(3b)	96	(5e)	67
6		(3c)	84	(5f)	60
7	(1g)	(3a)	96	(5g)	67
8		(3b)	95	(5h)	67
9		(3c)	93	(5i)	57



- a; R¹ = Bu, R² = R³ = H, R⁴ = Me
 b; R¹ = Bu, R² = R³ = H, R⁴ = Et
 c; R¹ = Bu, R² = H, R³ = R⁴ = Me
 d; R¹ = Et, R² = Me, R³ = H, R⁴ = Me
 e; R¹ = Et, R² = Me, R³ = H, R⁴ = Et
 f; R¹ = Et, R² = R³ = R⁴ = Me
 g; R¹R² = (CH₂)₄, R³ = H, R⁴ = Me
 h; R¹R² = (CH₂)₄, R³ = H, R⁴ = Et
 i; R¹R² = (CH₂)₄, R³ = R⁴ = Me

Scheme 1. Reagents and conditions: i, LDA in THF, -78°C ; ii, THF, -78°C ; iii, Ac₂O, -78°C to 20°C ; iv, Zn(Cu), aq. NH₄Cl, EtOH, 90°C .

The acetic nitronic anhydrides (4) thus obtained are easily converted to the corresponding alkylpyrroles (5) by reduction with zinc-copper couple and aqueous ammonium chloride in ethanol under reflux,[‡] wherein probably the following four-step reaction sequence is involved: (1) two consecutive reductions of acetic nitronic anhydride to imine *via* oxime; (2) iminoketone cyclisation; (3) dehydration. Thus, a variety of di-, tri-, and tetra-alkylpyrroles were prepared in 57–68% yields (Table 1). Taking into account that highly alkylated pyrroles are considerably susceptible to air oxidation,² the yields are acceptable. Indeed, the tetra-alkylpyrroles (entries 6 and 9) were found to be unstable in the extreme, although

[‡] The synthesis of 3-pyrrolecarboxylates by the direct reduction of nitronic acids has been reported, see ref. 8a. However, nitronic acids have generally been known to be unstable and readily decompose on standing (ref. 7, pp. 376–382 and ref. 8b). Indeed, we could not isolate the corresponding nitronic acids in good yields.

the products can be purified by rapid (within several minutes) silica gel flash chromatography.[§]

Regardless of the substitution pattern, it has been found that a wide variety of polyalkylpyrroles, including bicyclic ones, are readily derived from a combination of ketones and nitroalkenes. The present method provides a general route to alkylpyrroles.

A typical procedure is as follows. To a solution of LDA (1.2 mmol) in THF (3 ml) was added a solution of cyclohexanone (98 mg, 1 mmol) in THF (1 ml) at -78°C under argon. After being stirred for 30 min, a solution of nitropropene⁹ (131 mg, 1.5 mmol) in THF (0.5 ml) was added and the resulting mixture was further stirred for an additional 2 h at -78°C . Then acetic anhydride (204 mg, 2 mmol) was added and the mixture was allowed to warm up to room temperature over 2 h with stirring. The reaction mixture was partitioned between ethyl acetate and water, and the aqueous washes were extracted with ethyl acetate. The combined organic layers were washed with brine. Evaporation of the solvents left an oil, which was purified by silica gel column chromatography (ethyl acetate-hexane, 1:3) to give 220 mg (96% yield) of greenish 2-(2-acetyl-*aci*-nitropropyl)cyclohexanone as a stereoisomeric mixture.

To a solution of the above anhydride (220 mg, 0.97 mmol) in ethanol (3 ml) was added a mixture of zinc-copper couple (646 mg, 5 mmol), ammonium chloride (134 mg, 2.5 mmol), and water (0.4 ml), which was agitated well beforehand by a spatula, and the resulting mixture was stirred at 90°C for 1 h. The cooled reaction mixture was diluted with hexane and filtered through a short silica gel column with the aid of hexane. The filtrate was concentrated *in vacuo* and the residue was expeditiously purified by silica gel flash chromatography (ethyl acetate-hexane, 1:3) to afford 2-methyl-4,5,6,7-tetrahydro-indole (87 mg, 67% yield).

Received, 20th February 1989; Com. 9/00769E

References

- 1 A. R. Battersby, *Nat. Prod. Rep.*, 1987, **4**, 77; A. R. Battersby and E. McDonald, *Acc. Chem. Res.*, 1979, **12**, 14.
- 2 R. J. Sundberg, in 'Comprehensive Heterocyclic Chemistry,' Vol. 4, eds. C. W. Bird and G. W. H. Cheeseman, Pergamon Press, Oxford, 1984, pp. 313–353.
- 3 K. Inomata, H. Suhara, H. Kinoshita, and H. Kotake, *Chem. Lett.*, 1988, 813.
- 4 A. Meunier and R. Neier, *Synthesis*, 1988, 381.
- 5 Nitroalkenes have often been used in the synthesis of pyrrolecarboxylates and acylpyrroles but not alkylpyrroles. For reviews, see A. G. M. Barrett and G. G. Graboski, *Chem. Rev.*, 1986, **86**, 751; R. S. Varma and G. W. Kabalka, *Heterocycles*, 1986, **24**, 2645.
- 6 (a) D. Seebach, E. W. Colvin, F. Lehr, and T. Weller, *Chimia*, 1979, **33**, 1; (b) A. Yoshikoshi and M. Miyashita, *Acc. Chem. Res.*, 1985, **18**, 284.
- 7 A limited number of acetic nitronic anhydrides have been reported so far albeit they were prepared in poor yields. For a review, see A. T. Nielsen, in 'The Chemistry of the Nitro and Nitroso Groups,' Part 1, ed. H. Feuer, Interscience, New York, 1970, pp. 461–468.
- 8 (a) F. Boberg, K.-H. Garburg, K.-J. Görlich, E. Pipereit, and M. Ruhr, *Liebigs Ann. Chem.*, 1985, 239; (b) M. Ochiai, M. Arimoto, and E. Fujita, *Tetrahedron Lett.*, 1981, **22**, 1115.
- 9 M. Miyashita, T. Yanami, and A. Yoshikoshi, *Org. Synth.*, 1981, **60**, 101.

[§] It is necessary that tri- and tetra-alkylpyrroles are purified quickly without contact with air and should be handled as a solution rather than neat since they are tolerably stable in a solution.