Communications to the Editor

Chem. Pharm. Bull.
30(1) 366—369 (1982)

A FACILE ONE-POT SYNTHESIS OF DIACYLPYRROLES[1,3]

Shonosuke Zen*and Kazuho Harada
School of Pharmaceutical Sciences, Kitasato University
Shirokane, Minato-ku, Tokyo 108, Japan

Various diacylpyrrole derivatives (1) were synthesized in good yields by using ß-diketones (4) such as dibenzoylmethane in reaction with primary aliphatic nitro compounds (2) and acetyl chloride. The structures of 1 were established by chemical and spectral data. This reaction mechanism is discussed.

KEYWORDS——aliphatic nitro compound; ß-diketones; dibenzoylmethane; O-acylation; 1,3-dipolar cycloaddition; nitrile oxide; 1-azirine; pyrroles; N-methyl pyrroles

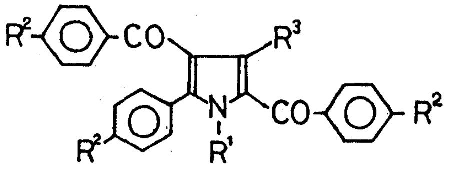
This communication deals with a convenient method of synthesizing diacylpyrrole derivatives (1) from ß-diketones (4) using primary aliphatic nitro compounds (2) and acetyl chloride. In our previous reports[2,4] a new route for generating nitrile oxides (3) was developed by the O-acylation of 2 with acetyl chloride in N,N-dimethylacetamide(DMA). One-pot synthesis of various heterocycles containing an N-O bond, i.e. isoxazolines etc., was presented to illustrate the usefulness of this method. During the course of studies, we found a novel synthetic reaction forming an unusual product (1) in the reaction of 3 with a dipolarophile, 4, such as dibenzoylmethane. This general procedure is shown as follows: 1.8g (8 mmol) of 4, 0.15 ml of acetyl chloride, and 4 ml of 1N sodium methoxide in methyl alcohol were added to a DMA solution of phenylnitromethane (2, 0.27g, 2 mmol) contained 2 ml of sodium methoxide solution with cooling at 0°C. It was stirred overnight at ambient temperature. Then ice water was added and the mixture was extracted with benzene, dried (Na_2SO_4) and concentrated to furnish crude crystals which were chromatographed on silica gel with benzene-ethyl acetate (20:1). This gave yellowish crystals, 0.31g of 2,4-dibenzoyl-3,5-diphenylpyrrole (1a) in a 36% yield [mp 234-235°C (chloroform-methyl alcohol); IRν_{max}^{KBr}cm^{-1}: 3270 (NH), 1660 (C=O); UVλ_{max}^{MeOH}nm (logε): 209 (4.67), 253 (4.61), 332 (4.33); ^{1}H-NMR($CDCl_3$)δ: 6.85-7.30 (20H, m, $4C_6H_5$), 10.17 (1H, s, NH, exchangeable with deuterium oxide); ^{13}C-NMR($CDCl_3$)δ: 123.2 (s,C(3)), 126.8 (s,C(4)), 130.3 (s,C(5)), 131.3 (s,C(2)), 187.8 (s,carbonylß), 194.2 (s, carbonylα); MS m/z: 427 (M^+)]. Furthermore, methylation of 1a by methyl iodide gave the corresponding N-methyl derivative (1Ma) in an 83% yield [mp 143-145°C (methyl alcohol); ^{1}H-NMR($CDCl_3$)δ: 3.83 (3H, s, N-CH_3); MS m/z: 441 (M^+)].

The following aliphatic nitro analogs (2) and ß-diketones (4) were employed in the above-mentioned procedure. 2: phenylnitromethane,[6] p-chlorophenylnitromethane,[6] p-tolylnitromethane,[7] and nitroethane; 4: dibenzoylmethane, bis(p-toluoyl)methane,[5] and bis(p-chlorobenzoyl)methane.[5] Subsequently, pyrrole derivatives (1a-1h) were synthesized and the results of extensive experiments are summarized in Table I.

The proposed reaction mechanism seems to be reasonable as shown in Chart 1. Initially, 1,3-dipolar cycloaddition of nitrile oxide (**3**) to dipolarophile, ß-diketone (**4**) gives the anticipated cyclo-adduct, isoxazoline (**5**), which undergoes elimination of benzoic acid to form 1-azirine (**6**). And another **4** reacts with its C=N bond to afford aziridine (**7**) and **8**, the enol-form of **7**, cyclizes to five-membered cyclic compound, **9**, via a fission of C-N bond of **8**. Finally, the dehydrated product, pyrrole (**1**) is yielded from **9** as observed by Ohta.8) This mechanism was confirmed by the following results: (i) Photoreaction9) of 3,5-diphenylisoxazole with **4** (R^2=H) under a Pyrex filtered light gave 2,4-dibenzoyl-3,5-diphenylpyrrole (**1a**)10) almost exclusively. (ii) Isolated 1-azirine **6a** (R^3=C_6H_5, R^2=H)11, 12) reacted with **4** (R^2=H) to give the corresponding **1a**.13) (iii) Isolated nitrile oxide **3b** (R^3=p-$CH_3C_6H_4$)14) reacted with **4** (R^2=H) to give both azirine **6b** and **1b**. (iv) In the ^{1}H-NMR spectra of pyrroles (**1b** and **1e**) and N-methyl pyrroles (**1Mb** and **1Me**), the characteristic p-methyl signals15) of the tolyl group located at the C-3 position were observed at δ 2.07-2.13 (3H, CH_3). These data also indicate that the α-carbon of **2** was introduced into the carbon atom at the C-3 ring.

A detailed study of the reaction is now in progress.

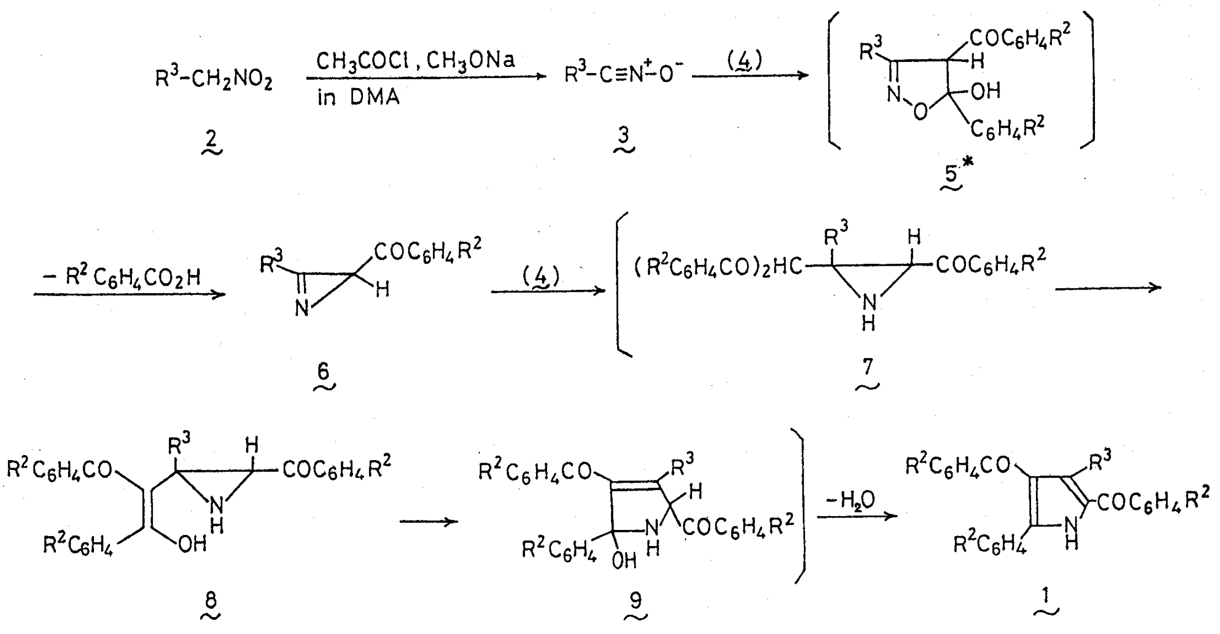
Table I. Yields, Melting Points, IR and ^{1}H-NMR Data of Pyrrole Derivatives (**1** and **1M**)



Compd.a)	R^1	R^2	R^3	Yield/%	mp/°C	IR νNH cm^{-1}	^{1}H-NMR NH	^{1}H-NMR N-CH_3
1a	H	H	C_6H_5	36	234-235	3270	10.17	---
1Ma	CH_3	H	C_6H_5	83	143-145	----	---	3.82
1b	H	H	p-$CH_3C_6H_4$	49	230-231	3250	10.20	---
1Mb	CH_3	H	p-$CH_3C_6H_4$	75	142-143	----	---	3.80
1c	H	H	p-ClC_6H_4	45	232-233	3240	10.05	---
1Mc	CH_3	H	p-ClC_6H_4	80	166-168	----	---	3.80
1d	H	CH_3	C_6H_5	42	227-228	3240	10.20	---
1Md	CH_3	CH_3	C_6H_5	80	164-166	----	---	3.80
1e	H	CH_3	p-$CH_3C_6H_4$	56	231-233	3240	10.22	---
1Me	CH_3	CH_3	p-$CH_3C_6H_4$	82	162-164	----	---	3.77
1f	H	Cl	C_6H_5	33b)	265-267	3240	10.53	---
1Mf	CH_3	Cl	C_6H_5	85	195-196	----	---	3.75
1g	H	Cl	p-ClC_6H_4	29	264-266	3240	10.50	---
1Mg	CH_3	Cl	p-ClC_6H_4	80	194-196	----	---	3.73
1h	H	H	CH_3	5b)	175-176	3240	---	---

a) All compounds gave satisfactory microanalyses.

b) Reacted at 80°C.



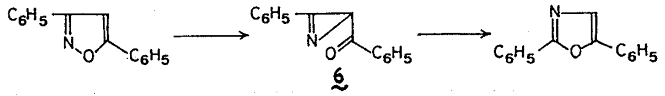
$(\underset{\sim}{4})$: $(R^2C_6H_4CO)_2CH_2 \rightleftharpoons R^2C_6H_4C(OH){=}CHCOC_6H_4R^2$

*By dehydration from $\underset{\sim}{5}$, 4-acylisoxazoles were obtained as repoted in Ref. 2.

Chart 1

REFERENCES AND NOTES

1) The Synthetic Reaction of Aliphatic Nitro Compounds. XIX; Presented in part at the 8th International Congress of Heterocyclic Chemistry, Graz (Austria), August 1981, Abstr.p. 499; Part XVIII of this series is ref.2.
2) K. Harada, E. Kaji, and S. Zen, Nippon Kagaku Kaishi, 1981, 1195.
3) Melting points are uncorrected; ^{1}H- and ^{13}C-NMR spectra were measured using TMS as an internal standard.
4) E.Kaji, K. Harada, and S. Zen, Chem. Pharm. Bull., 26, 3254(1978); K. Harada, E. Kaji, and S. Zen, ibid., 28, 3296(1980).
5) A. Sieglitz and O. Horn, Chem. Ber., 84, 607(1951).
6) N. Kornblum, H. O. Larson, R. K. Blackwood, D. C. Mooherry, E. P. Olivets, and G. E. Garakam, J. Am. Chem. Soc., 78, 1497(1956).
7) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, J. Am. Chem. Soc., 77, 6269(1955).
8) S. Sato, H. Kato, and M. Ohta, Bull. Chem. Soc. Jpn., 40, 2936(1967).
9) a) Generally, the photorearrangement of 3,5-diphenylisoxazole gives 2,5-diphenyloxazole by light of 3130Å wavelength via an intermediate, 1-azirine ($\underset{\sim}{6}$, R^2=H, R^3=C_6H_5) :



P. Beak and W. R. Messer, "Organic Photochemistry" Vol. II, ed. by O. L. Chapman, Marcel Dekker, New York, 1969, p. 136.

b) Bis(2,4-pentanedionato)nickel(Ni(acac)$_2$) was added in the reaction as catalyst.

10) Similarly, 3-p-tolyl- and 3-p-chlorophenyl-5-phenylisoxazole also gave the corresponding pyrroles (**1b** and **1c**) in the photoreaction.

11) E. F. Ullman and B. Singh, J. Am. Chem. Soc., 88, 1844(1966).

12) Similarly, 1-azirine **6b** (R^3=p-$CH_3C_6H_4$, R^2=H) and **6c** (R^3=p-ClC_6H_4, R^2=H)13) also gave the corresponding **1b** and **1c**; both **6b** and **6c**, syrup, were confirmed by the method of UV and IR as reported by Ullman (ref. 11).

13) P. F. S. Filho and U. Schuchardt, Angew. Chem. Int. Ed. Engl., 16, 647(1977): They obtained a number of pyrroles by the reaction of 1-azirine with ketone, which was activated by Ni(acac)$_2$. This result is closely related to the above-mechanism reported in the present paper.

14) G. Barbaro, A. Battaglia, and A. Dondoni, J. Chem. Soc., B, 1970, 588; A. Quilico "Five and Six-membered Compounds with Nitrogen and Oxygen" ed. by R. H. Wiley, Interscience, New York, 1962, p. 21.

15) Signals of p-methyl groups of C-2 and C-4 of pyrroles and N-methyl derivatives (**1d**, **1e**, **1Md**, **1Me**) were observed at one signal, δ 2.23-2.28 and also, that of C-5 were observed at 2.33-2.38.

(Received October 28, 1981)