SYNTHESIS OF 4-ACYLISOXAZOLE-5-CARBOXYLATES VIA 1,3-DIPOLAR CYCLOADDITION REACTION OF β-ACYLPYRUVATES WITH NITRILE OXIDES IN THE ABSENCE OF BASE

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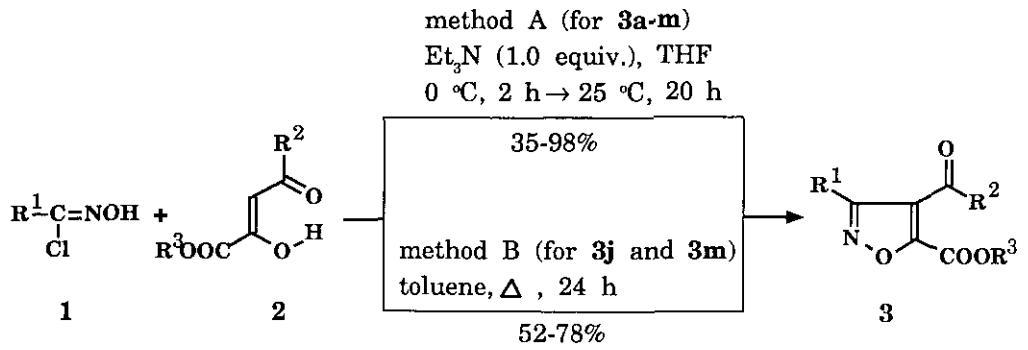
Abstract - The fully substituted isoxazole derivatives **3** were prepared in moderate to high yields *via* the cycloaddition reaction of nitrile oxides with β-acylpyruvates **2**. β-Acylpyruvates, unlikely ordinary β-diketones, show high dipolarophilic reactivity toward nitrile oxides in the absence of base.

1,3-Dipolar cycloaddition reaction of nitrile oxides with olefins, acetylenes, and active methylene compounds such as β-diketones is well known. [1] The reactions of benzonitrile oxides with β-diketones gave isoxazoles only in the presence of base, suggesting that the reaction involves 1,3-dipolar cycloaddition of nitrile oxide to the enol form of the β-diketone, followed by subsequent dehydration of the resulting Δ^2-isoxazolin-5-ol, which could not be isolated.[2,3] Tetrahydrobenzisoxazoles were synthesized by the reaction of nitrile oxides with 1,3-cyclohexanediones in the presence of excess triethylamine.[4]

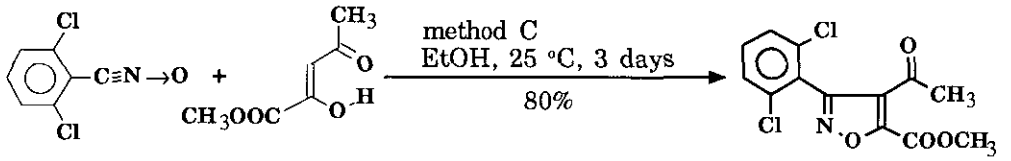
We now wish to report herein the synthesis of new isoxazoles from the 1,3-dipolar cycloaddition reaction of nitrile oxides with β-acylpyruvates and the high dipolarophilic activity of β-acylpyruvates.

Hydroximoyl chlorides **1a-j**, the precursors for nitrile oxides *in situ* and 2,6-dichlorobenzonitrile oxide (**4**) were easily prepared according to the published methods.[5-10] β-Acylpyruvates **2a** and **2k-m** were prepared from acetone, acetophenone, and 2-butanone with diethyl oxalate by the reported procedures, respectively.[11,12] β-Acylpyruvates **2a-m** reacted, under conditions of the absence of base, with nitrile oxides generated *in situ* from hydroximoyl chlorides **1a-j** (methods A, B) or freshly prepared nitrile oxide **4** (method C), furnished 4-acylisoxazole-5-carboxylates **3a-m** in moderate to high yields. The results were summarized in the Table.



Entry	R^1	R^2	R^3	Entry	R^1	R^2	R^3
a	CF_3	Me	Me	**h**	2-Cl, 5-$NO_2C_6H_3$	Me	Me
b	COMe	Me	Me	**i**	2-ClC_6H_4	Me	Me
c	COOEt	Me	Me	**j**	2,6-$Cl_2C_6H_3$	Me	Me
d	COPh	Me	Me	**k**	2,6-$Cl_2C_6H_3$	Ph	Me
e	Ph	Me	Me	**l**	2,6-$Cl_2C_6H_3$	Et	Me
f	3-$NO_2C_6H_4$	Me	Me	**m**	2,6-$Cl_2C_6H_3$	Me	Et
g	4-ClC_6H_4	Me	Me				

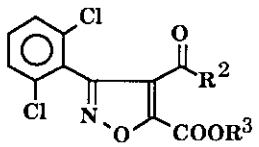
Initially, we examined cycloaddition reactions of **4** with various 1,3-dicarbonyl compounds such as ethyl acetoacetate, 2,4-pentanedione, 1,3-cyclohexanedione, and methyl acetopyruvate (**2a**) without using any base in order to evaluate their dipolarophilic activities. A slight excess amount (1.1 equiv.) of **4** was added to ethanol solution of 1,3-dicarbonyl compound and the mixture was stirred for 3 days at room temperature. While **4** and ethyl acetoacetate gave no reaction, **4** and 2,4-pentanedione or 1,3-cyclohexanedione afforded trace amounts of the corresponding isoxazoles. In contrast, in the case of **2a** methyl 3-(2,6-dichlorophenyl)-4-acetylisoxazole-5-carboxylate (**3j**) was obtained in 80% yield (method C).



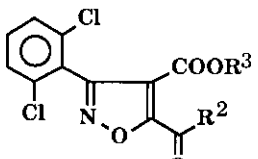
To our knowledge, this is the first example of the cycloadditon reaction of nitrile oxides with β-acylpyruvates in the absence of base. Compared to the nitrile oxides

thermally generated (method B)[13] or isolated (method C), the nitrile oxides generated *in situ* (method A)[14] from the treatment of 2,6-dichlorobenzohydroximoyl chloride (**1j**) with triethylamine (1.0 equiv.) gave the best yield (89%) of the product **3j**. The examination of the influence of base on the cycloaddition reaction using 5 fold excess of triethylamine in the reaction of **1j** with **2a** resulted in no difference in yields of the isoxazole **3j** compared to those of the isoxazole prepared under conditions of the absence of the base during cyclization reactions. On the basis of our observations, it can be assumed that the high reactivity of β-acylpyruvates is attributed partly to the high enol content[15] and partly due to the electron withdrawing substituents, alkoxycarbonyl groups, resulting in electron deficiency at the enol double bond and accelerating the rate of reaction.[1]

It was noteworthy that regioisomers of the 4-acylisoxazole-5-carboxylates **3a-k** were not detected in all cases except in the cases of **3l, m**. The reaction of 2,6-



3l, m



5l, m

dichlorobenzonitrile oxide with β-acylpyruvates **2l, m** gave the corresponding mixtures of regioisomers, **3l, m** and **5l, m** (see Table). The ratios of **3l/5l** and **3m/5m** were estimated respectively by integration of the alkoxy signals on ^{1}H nmr spectra.[16,17] Attempts to separate these regioisomers were unsuccessful by preparative tlc or column chromatography on silical gel. The substituent effects of β-acylpyruvates on regioselectivity are under investigation.

In conclusion the work described in this paper clearly demonstrates that β-acylpyruvates show high dipolarophilic characters toward nitrile oxides without the aid of base in the 1,3-dipolar cycloaddition reaction.

EXPERIMENTAL

4-Acylisoxazole-5-carboxylates (3a-m); General Procedure:

Method A (for **3a-m**): To a stirred solution of β-acylpyruvate **2** (10 mmol) and hydroximoyl chloride **1** (10 mmol) in dry THF (40 ml) is added dropwise a solution of triethylamine (10 mmol) in dry THF (15 ml) at 0 °C over a period of 2 h. The reaction mixture is further stirred 20 h at room temperature. After filtered

Table. 4-Acylisoxazole-5-carboxylates **3a-m** prepared[a]

Product	Method	Yield (%)	mp[b] (°C)	Molecular Formular	^{1}H-Nmr (acetone-d_6/TMS)[c] δ, J(Hz)	Ir[d] ν(cm^{-1})	Ms (20eV)[e] m/z (%)	Analyses[f] Calcd/Found(%) C	H	N
3a	A	74	oil	$C_8H_6F_3NO_4$	2.79(s, 3H); 3.99(s, 3H)	1751	237(M^+,11)	40.52	2.55	5.91
				(237.1)		1701		40.05	2.50	5.78
3b	A	45	49-51	$C_9H_9NO_5$	2.67(s, 3H); 2.68(s, 3H);	1724	211(M^+, 7)	51.19	4.30	6.63
				(211.1)	3.89(s, 3H)	1609		51.18	4.28	6.58
3c	A	81	oil	$C_{10}H_{11}NO_6$	1.36(t, J=7.1, 3H); 2.71(s, 3H);	1748	241(M^+, 5)	49.80	4.60	5.81
				(241.1)	3.88(s, 3H); 4.41(q, J=7.1, 2H)	1628		49.62	4.62	5.77
3d	A	35	76-80	$C_{14}H_{11}NO_5$	2.79(s, 3H); 3.69(s, 3H);	1763	273(M^+, 1)	61.54	4.06	5.13
				(273.2)	7.62-8.22(m, 5H)	1697		61.51	4.07	5.43
						1651				
3e	A	95	83-85	$C_{13}H_{11}NO_4$	2.75(s, 3H); 3.43(s, 3H);	1748	245(M^+, 5)	63.67	4.52	5.71
				(245.2)	7.51-7.58(m, 5H)	1690		63.53	4.52	5.76
3f	A	98	94-96	$C_{13}H_{10}N_2O_6$	2.78(s, 3H); 3.64(s, 3H);	1736	290(M^+, 4)	53.80	3.47	9.65
				(290.2)	7.85-8.47(m, 4H)	1674		53.65	3.49	9.59
3g	A	79	125-126	$C_{13}H_{10}ClNO_4$	2.75(s, 3H); 3.57(s, 3H);	1748	279(M^+, 8)	55.83	3.60	5.01
				(279.6)	7.58(s, 4H)	1686		55.96	3.68	5.04
3h	A	90	78-80	$C_{13}H_9ClN_2O_6$	2.82(s, 3H); 3.68(s, 3H);	1748	324(M^+, 3)	48.09	2.79	8.63
				(324.6)	7.92-8.49(m, 3H)	1674		48.24	2.79	8.70
3i	A	71	117-119	$C_{13}H_{10}ClNO_4$	2.78(s, 3H); 3.50(s, 3H);	1748	279(M^+, 3)	55.83	3.60	5.01
				(279.6)	7.53-7.59(m, 4H)	1690		55.78	3.63	5.02
3j	A	89	109-111	$C_{13}H_9Cl_2NO_4$	2.61(s, 3H); 4.10(s, 3H);	1740	314(M^+, 4)	49.71	2.89	4.46
	B	78		(314.1)	7.62(m, 3H)	1686		49.71	2.85	4.43
	C	80								

Table. Continued

3k	A	50	95-96	$C_{18}H_{11}Cl_2NO_4$ (376.1)	3.73(s, 3H); 7.51-7.93(m, 8H)	1744 1667	340(M^+-Cl,100)	57.47 57.41	2.95 2.93	3.72 3.75
3l+5l (35:65)	A	44	oil[g]	$C_{14}H_{11}Cl_2NO_4$ (328.1)	for **3l**: 1.04(t, J=7.2, 3H); 3.04(q, J=7.2, 2H); 4.09(s, 3H); 7.61-7.63(m, 3H) for **5l**: 1.41(t, J=7.5, 3H); 3.24(q, J=7.5, 2H); 3.55(s, 3H); 7.61-7.63(m, 3H)	1748 1690	328(M^+, 25)	51.24 51.24	3.38 3.41	4.27 4.34
3m+5m (95:5)	B	52	84-86[g]	$C_{14}H_{11}Cl_2NO_4$ (328.1)	for **3m**: 1.46(t, J=7.2, 3H); 2.61(s, 3H); 4.57(q, J=7.2, 2H); 7.62(s, 3H) for **5m**: 1.25(t, J=7.2, 3H); 2.90(s, 3H); 4.04(q, J=7.2, 2H); 7.62(s, 3H)	1736 1694	328(M^+, 3)	51.24 51.32	3.38 3.37	4.27 4.28

[a] All compounds are new.

[b] Not corrected, measured with a Thomas-Hoover melting point apparatus.

[c] Recorded on a Bruker AM-300 Nmr Spectrometer.

[d] Recorded on a Perkin-Elmer 283 Infrared Spectrophotometer with KBr pellet except for **3a, 3c,** and **3l+5l** (neat).

[e] Obtained on a Shimadzu QP 1000 Spectrometer.

[f] Recorded on a Perkin-Elmer 240C Elemental Analyzer.

[g] The ratio of the regioisomers is determined by ^{1}H-nmr spectroscopy.

off triethylamine hydrochloride, the solvent is removed under reduced pressure to give crude product **3**. Pure product is isolated by column chromatography on silica gel using 40% CH_2Cl_2 in petroleum ether as eluent.

Method B (for **3j** and **3m**): A solution of β-acylpyruvate **2** (10 mmol) and hydroximoyl chloride **1** (10 mmol) in dry toluene (50 ml) is heated to reflux for 24 h. After removal of the solvent *in vacuo*, column chromatography of the crude product on silica gel (40% CH_2Cl_2 in petroleum ether) afforded pure product **3**.

Methyl 3-(2,6-dichlorophenyl)-4-acetylisoxazole-5-carboxylate (3j); Typical Procedure:

Method C: Methyl acetopyruvate (**2a**; 10.0 g, 69.5 mmol) and freshly prepared 2,6-dichlorobenzonitrile oxide (**4**; 14.4 g, 76.6 mmol) are dissolved in absolute EtOH (150 ml), and the mixture is stirred for 48 h at room temperature during which time a crystalline product **3j** is appeared in the reaction mixture. After further 24 h stirring precipitated solid is separated by filtration, washed with small volumes of EtOH, and dried *in vacuo* to give the product **3j** (11.3 g). Another crude crop (7.5 g) is obtained from the filtrates and washings after silica gel column chromatography using 40% CH_2Cl_2 in petroleum ether as eluent. Recrystallization of the crude product from n-hexane affords analytically pure **3j** (17.5 g, 80%).

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. P. Caramella and P. Grunanger, '1,3-Dipolar Cycloaddition Chemistry,' ed. by A. Padwa, John Wiely & Sons, New York, 1984.
2. A. Quilico and G. Speroni, *Gazz. Chim. Ital.*, **1946**, *76*, 148.
3. F. P. Doyle, J. C. Hanson, A. A. W. Long, J. H. C. Nayler, and E. R. Stove, *J. Chem. Soc.*, **1963**, 5838.
4. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and A. G. Pozdeyev, *Synthesis*, **1978**, 43.
5. K. Tanaka, H. Masuda, and K. Mitsuhashi, *Bull. Chem. Soc. Jpn.*, **1984**, *57*, 2184.

6. A. P. Kozikowski and M. Adamczyk, *J. Org. Chem.*, **1983**, *48*, 366.
7. G. Hesse and G. Krehbiel, *Chem. Ber.*, **1955**, 130.
8. N. Levin and W. H. Hartung, *Org. Synth., Coll. Vol., III.* **1955**, 191.
9. K. C. Liu, B. R. Shelton, and R. K. Howe, *J. Org. Chem.*, **1980**, *45*, 3916.
10. C. Grundmann and J. M. Dean, *J. Org. Chem.*, **1965**, *30*, 2809.
11. C. S. Marvel and E. E. Dreger, *Org. Synth., Coll. Vol., I.* **1941**, 238.
12. H. Keskin and V. Yanco, *Istanbul Univ. Fen Fak. Mecm., Seri C* **1966**, *31*, 147 (*Chem. Abstr.*, **1968**, *69*, 86298n).
13. P. Caldirola, M. DE. Amici, and C. DE. Micheli, *Heterocycles,* **1985**, *23*, 2479.
14. M. Christl and R. Huisgen, *Chem. Ber.*, **1973**, *106*, 3345.
15. R. N. Henrie II, R. W. Creekmore, and W. H. Yeager, *J. Org. Chem.*, **1988**, *53*, 5977.
16. M. Christl, R. Huisgen, and R. Sustmann, *Chem. Ber.*, **1973**, *106*, 3275.
17. The structures of the regioisomers **3l, m** and **5l, m** were differentiated by taking into account the chemical shifts of alkoxy signals of esters on ^{1}H-nmr spectra. Alkoxy signals of both **3l** and **3m** are downfield shifted while those of **5l** and **5m** are upfield shifted because of the deshielding effect of the oxygen atom on the isoxazole nucleus.[16] In addition, the structures of **3a-k** were strongly supported by the chemical degradation of **3g** as an example into 3-(4-chlorophenyl)-4-acetylisoxazole *via* hydrolysis followed by decarboxylation and its ^{1}H-nmr structural assignment. The presence of a proton signal at 9.90 ppm in the degraded product indicated that the proton was attached on C-5 based on the fact that the signal for a proton on C-5 appeared downfield about 2 ppm than that for C-4 proton which generally appeared in the range of 6.0 - 7.5 ppm depending on the substituents in the isoxazoles (for example, see: reference 18). From these results, we assumed that the structures of **3a-k** could be assigned as 4-acylisoxazole-5-carboxylates rather than 5-acylisoxazole-4-carboxylates. Preparation of 3-(4-chlorophenyl)-4-acetylisoxazole as a degraded product of **3g**: Compound **3g** (280 mg, 1 mmol) was treated with aqueous NaOH and then acidified with aqueous HCl. The reaction mixture was extracted with EtOAc followed by usual work-up afforded the crude carboxylic acid derivative, which was decarboxylated under reduced pressure (20 torr, 150 °C) and chromatographed on silica gel column to give the desired 3-(4-chlorophenyl)-4-acetylisoxazole (69 mg, 31%);

^{1}H-nmr ($CDCl_3$) δ2.78 (s, 3H), 7.30-7.75 (m, 4H), 9.90 (s, 1H); ms (m/z, %) 221 (M^+, 12), 178 (29), 43 (100).

18. B. J. Wakefield and D. J. Wright, 'Advances in Heterocyclic Chemistry: Isoxazole Chemistry Since 1963,' Vol. 25, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, Inc., London, 1979, p. 201.

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