FORMATION OF NOVEL ISOXAZOLINE SPIRO COMPOUNDS BY A REACTION OF ARYL SUBSTITUTED α-NITROACRYLATES WITH TITANIUM TETRACHLORIDE AND TOLUENE[1,2]

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Abstract New spiroisoxazoline derivatives were synthesized *via* novel cyclization of arylsubstituted α-nitroacrylates (naphthyl and phenanthryl analogues) with $TiCl_4$ and toluene. The structural determination by single crystal X-ray analysis is reported.

This communication is dealing with a novel one-step synthesis of new spiroisoxazoline derivatives by a reaction of aryl(fused ring type)substituted α-nitroacrylates[3] with $TiCl_4$ in toluene . Ethyl 3-substituted naphthyl or phenanthryl-2-nitroacrylates (**1**)[4,5] reacted with toluene in the presence of $TiCl_4$ to give novel products, tolylated spiroisoxazolines (**2**)[6] unexpectedly (Scheme 1).

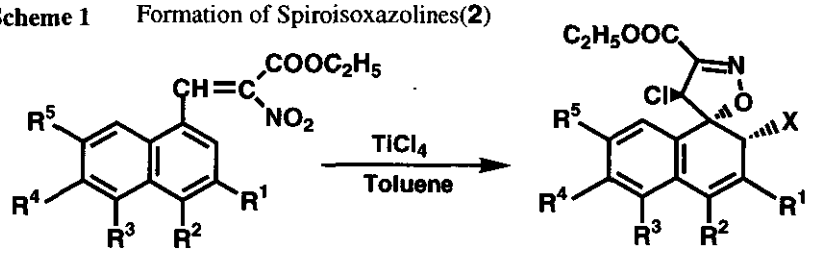
Typical procedure is as follow. $TiCl_4$(0.22 ml, 2 mmol) was added to a solution of ethyl 2-nitro-3-(4'-methyl-1'-naphthyl) acrylate(**1b**, 285 mg, 1 mmol) in toluene(10 ml) at 0°C. The reaction mixture was stirred during two hours, followed by addition of water and extraction with dichloromethane. Purification by column chromatography on silica gel (hexane:ethyl acetate=10:1) gave product (**2b**) as colorless prisms in 90.1% yield.

By similar procedure, the corresponding products (**2**)[7] were given from **1** respectively. The results are summarized in Scheme 1.

The structure of **2a** was confirmed as follows: **2a**: mp 79.0-82.0°C (recrystallized from CH_3OH). The ^1H nmr spectrum of **2a** showed signals assignable to a singlet proton of CHCl;4-position of isoxazoline ring

(δ=5.19 ppm), and naphthalene ring (δ=4.53 ppm, d, J=6.5 Hz, δ=6.24 ppm, dd, J=9.0 and 6.5 Hz, δ= 6.74 ppm, d, J=6.5 Hz). The carbon signals of isoxazoline moiety were assigned from long-range selective proton decoupling (LSPD)method. ^{13}C Nmr spectrum showed isoxazoline ring moiety at δ=67.9 (C-4), 94.9 (C-5) and 151.5 ppm (C-3), and naphthalene ring moiety at δ=44.9 (C-2'), 128.1 (C-4'), 131.2 ppm (C-3'). When the H-4 methine of isoxazoline ring was irradiated, NOE enhancements(0.5 % and 1.1%) were observed in ^{1}H resonance of H-2' and H-8' methine (δ=6.84 ppm) of naphthalene ring.

Scheme 1 Formation of Spiroisoxazolines(**2**)



1 **2**

Substrate	R^1	R^2	R^3	R^4	R^5	Product		Yield(%)
1a	H	H	H	H	H	2a	X=*p*-Tolyl	40.1
						3a		(ca.40)*
1b	H	CH_3	H	H	H	2b	X=*p*-Tolyl	90.0
1c	H	Cl	H	H	H	2c	X=*p*-Tolyl	76.7
						2c'	X=Cl	7.0
1d	(-CH=CH-)$_2$		H	H	H	2d	X=*p*-Tolyl	49.9
						2d'	X=Cl	3.6
1e	H	H	(-CH=CH-)$_2$		Br	2e	X=*p*-Tolyl	61.1

* determined by ^{1}Hnmr in the crude product.

Table 1 Selected Torsional Angles(ϕ(°)) and Bond Lengths(Å) of **2a**.

	(1/ϕ(°))		(1/Å)
Cl(1)-C(4)-C(5)-(C2')	-25.6(3)	O(1)-N(1)	1.385(3)
C(1")-C(2')-C(5)-C(4)	157.9(3)	N(1)-C(3)	1.276(3)
C(1")-C(2')-C(3')-C(4')	99.5(4)	Cl(1)-C(4)	1.796(3)
N(1)-C(3)-C(4)-C(5)	17.1(3)	C(4)-C(5)	1.536(3)
O(1)-C(5)-C(2')-C(3')	168.9(3)	C(5)-C(8a')	1.519(4)
C(5)-C(2')-C(3')-C(4')	-27.7(5)	C(5)-C(2')	1.521(4)

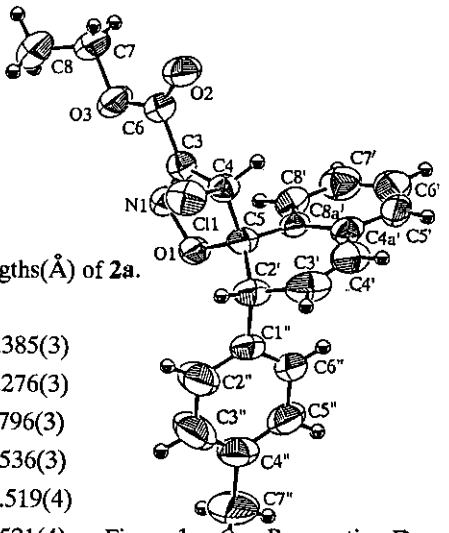


Figure 1 Perspective Drawing of **2a**

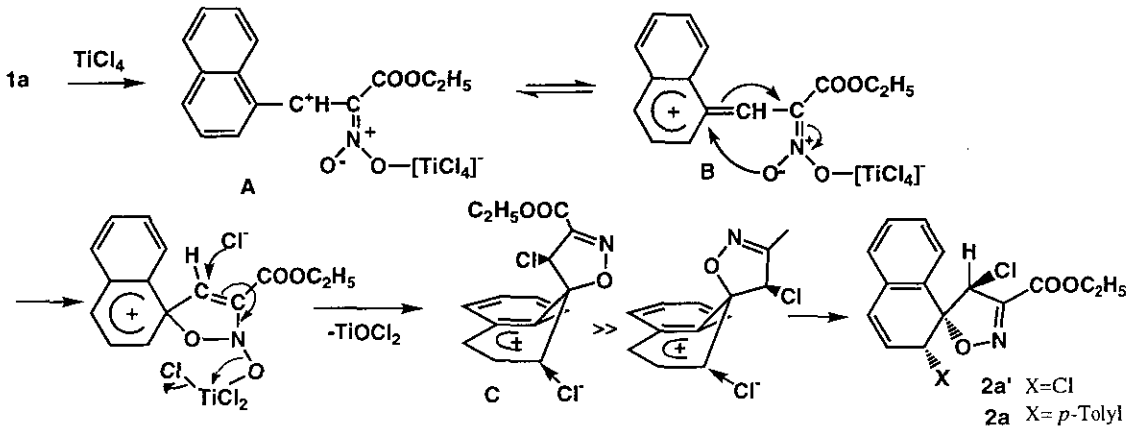
The structure of **2a**, in particular, the stereochemistry of 4-and 2'-positions was determined by single crystal X-ray analysis[8]. Thus, the relative structure of **2a** was determined to (R^*)-4-chloro-3-ethoxycarbonyl-2'-tolylspiro [isoxazole-5(4*H*),1'(2'*H*)naphthalene], illustrated in Figure 1. The selected dihedral angles and the bond lengths are listed in Table 1.

On the other hand, **2c'** reacted with toluene in the presence of $TiCl_4$ to give **2c** also in reasonable yield. Therefore it seems reasonable to assume that the formation of **2c** may proceed *via* **2c'** from **1c**. Reactivity of arylation was examined in above reaction with **1a** for aromatic solvents. When using benzene, both 2'-phenylated spiroisoxazoline (X=phenyl)[10] and 2'-chlorinated spiroisoxazoline (X=Cl, **2a'**)[11] were given in 9.9 and 2.7 % yields respectively. And however with chlorobenzene, the corresponding chlorophenylated spiroisoxazoline was not detected but **2a'** was given in 1.2% yield. Thus, benzene of slightly lower nucleophilicity failed to give **2** in synthetically useful yield. As a result, toluene seems to be favorable as a reactant.

A plausible reaction pathway to form **2** with $TiCl_4$ from **1** is shown in Scheme 2. **1a** proceeds *via* initial electrophilic attack of $TiCl_4$ to intermediate **A**, which converts to **B** followed by cyclization. Next, chlorination of β carbon and cleavage of the N-O bond cause the formation of intermediate **C** with an elimination of $TiOCl_2$. Subsequently, after chlorination to 2'-position of naphthalene ring, **2a'**(X=Cl) converts to **2a** by Friedel-Crafts reaction. The predominant formation of **2a'** is rationalized in terms of steric control of approach of chloride as shown in structure **C**. Another stereoisomers were not isolated.

Analogues **2** in Scheme 1 were given by similar process.

Scheme 2 A Proposed Reactin Mechanism for formation of **2** from **1**



In the reaction of **1a** with $TiCl_4$, the products were of two types; spiroisoxazoline compounds(**2a**) and ethyl 3-chloro-3-(4'-chloro-1'-naphtyl)-2-hydroxyiminopropionate(**3a**).[6] But **1b** gave sole product **2b**. The product may be controlled by aryl groups of **1**.

Applications of this synthetic reaction are currently under investigation.

REFERENCES AND NOTES

1 The Synthetic Reaction of Aliphatic Nitro Compounds XXVIII (part XXVII: Ref.2).

2 S. Hirotani and S. Zen, *Nippon Kagaku Kaishi*, **1993**, 948.

3 S. Hirotani and S. Zen, *Chem. Pharm. Bull.*, 1983, **31**, 2944.

4 These acrylates were employed a mixture of *E* and *Z*.

5 These were synthesized by method of A. Dornow and H. Menzel(*Ann.*, 1954, **588**, 40).

1b, yield 58.8%, mp 61.0-62.0°C(mixture of *Z:E*=1.7:1). **1c**, yield 70.0%, mp 70.0-72.0°C(mixture of *Z:E*=4:3), **1d**, yield 76.2% *Z*: mp 117.5-119.5°C(from benzene); *E*: mp 95.5-98.0°C(from benzene-petroleum ether), **1e**, yield 67.7%, mp 114.0-116.0°C(mixture of *Z:E*=4:1) .

6 When using dichloromethane as aprotic dipolar solvent in this reaction, ethyl 3-chloro-3-(4'-chloro-1'-naphthyl)-2-hydroxyiminopropionate (**3a**) was obtained from **1a** as sole main product (reported in ref. 2). This result is closely related to the method reported in the present paper, whereby, however spiroisoxazoline derivatives are obtained(Scheme 1).

7 **2a**: Anal. Calcd for $C_{22}H_{20}NO_3Cl$: C, 69.20; H, 5.28; N, 3.67; Cl, 9.28. Found: C, 69.02; H, 5.26; N, 3.54; Cl, 9.38. Ms (m/z) : 383(M^++2, 7.5), 381(M^+, 21.1), 346(100), 218(47.4). Ir(KBr, cm^{-1}): 1720, 1570. ^1H Nmr(400 Mz, $CDCl_3$, δ, ppm): 1.37(3H, t, *J*=7.0 Hz, CH_3), 2.27(3H, s, CH_3), 4.34 and 4.36(each 1H, dq, *J*=7.0 Hz and 4.0 Hz, OCH_2), 4.53(1H, d, *J*=6.5 Hz, H-2'), 5.19(1H, s, H-4), 6.24(1H, dd, *J*=9.0 Hz and 6.5 Hz, H-3'), 6.74(1H, d, *J*=6.5 Hz, H-4'), 6.84(1H, d, *J*=7.8 Hz, H-8'), 6.99(4H, s, tolyl H), 7.14(1H, td, *J*=7.8 Hz and 1.5 Hz, H-7'), 7.25(1H, dd, *J*=7.5 Hz and 1.3 Hz, H-5'), 7.32(1H, td, *J*=7.8 Hz and 1.3 Hz, H-6'). ^{13}C Nmr(100 MHz, $CDCl_3$, δ, ppm): 14.0(CH_3), 21.0(CH_3), 44.9(C-2'), 62.5(OCH_2), 67.9(C-4), 94.9(C-5), 124.5(C-8'), 127.3(C-5'), 128.1(C-4'), 128.4(C-7'), 129.0(tolyl C-3" and C-5"), 129.3(C-6'), 129.5(tolyl C-2" and C-6"), 130.7(tolyl C-1"), 131.2(C-3'), 131.7(C-8a'), 132.9(C-4a'), 137.4(tolyl C-4"), 151.5(C-3), 158.9(COO).

2b: mp 134.0–134.5°C(CH_2Cl_2–CH_3OH), ^1H and ^{13}C nmr($CDCl_3$, δ) of CHX and CHCl(isoxazoline ring), 4.46(H–2') and 44.7(C–2'), 5.16(H–4) and 67.9(C–4), **2c**: mp 134.5–135.5°C(CH_2Cl_2–CH_3OH), δ 4.58 and 45.8, 5.22 and 67.6, **2c'**: 179.0–180.0°C(acetone–CH_3OH), δ 5.34 and 55.0, 5.11 and 65.6, **2d**:mp 71.0–73.0°C(ether–CH_3OH), δ 5.02 and 49.5, 5.00 and 67.1, **2d'**: mp 176.0–176.5°C(ether–petroleum ether), δ 5.73 and 58.7, 4.90 and 65.0, **2e**: mp 220.0–222.0°C(CH_2Cl_2–CH_3OH), δ 4.64 and 44.5, 5.28 and 68.4.

8 **X–Ray Analysis of 2a** A colorless prism crystal of approximately 0.3 x 0.5 x 0.2 mm was mounted on a Rigaku AFC–5R diffractometer and cell parameter and the intensity data were measured with graphite monochromated Cu Kα radiation. Crystal data for **2a**:$C_{22}H_{20}NO_3Cl$, MW=381.86, triclinic, space group $p1$, μ for Cu Kα=18.91cm^{-1}, a= 11.170(1) Å, b= 11.364 (1) Å, c= 9.3879(9) Å, α= 109.487(7)°, β= 112.665(7)°, γ=97.808(9)°, V= 987.5(5) Å^3, Z=2, Dcalc=1.284 gcm^{-3}. Of the total of 3792 reflections up to the 2θ rang of 140.2°, 3597 were measured as above the 3σ(I) level and were used for the structure determination. Approximate atomic coordinations were obtained by the direct method using program MITHRIL[9] and subsequently they were refined by the full–matrix least–squares method.

The final R value was 0.056.

9 C. J. Gilmore: MITHRIL–an integrated direct methods computer program. *J. Appl. Cryst.*, 1984, **17**, 42, Univ. of Glasgow, Scotland.

10 mp 155.5–156.5°C(CH_2Cl_2–CH_3OH), ^1H and ^{13}C nmr($CDCl_3$, δ) of CHX and CHCl(isoxazoline ring), 4.56(H–2') and 45.2(C–2'), 5.19(H–4) and 67.9(C–4).

11 mp 161.0–162.9°C(benzene–hexane), ^1H and ^{13}C nmr($CDCl_3$, δ) of CHX and CHCl(isoxazoline ring), 5.30(H–2') and 54.3(C–2'), 5.05(H–4) and 65.8(C–4).

12 All new compounds in this paper gave satisfactory spectral and analytical data.

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