

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 -nitroacrylates³ 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).

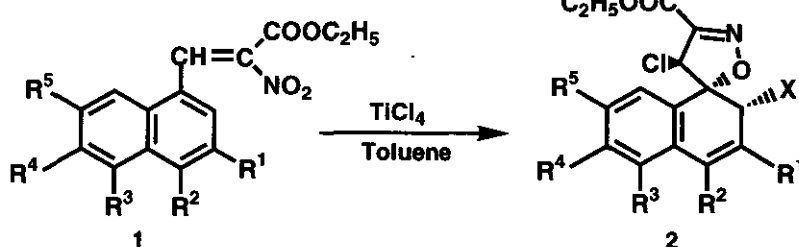
Typical procedure is as follow. TiCl_4 (0.22 ml, 2 mmol) was added to a solution of ethyl 2-nitro-3-(4'-methyl-1'-naphthyl) acrylate (**1b**, 285 mg, 1 mmol) in toluene (10 ml) at 0°C. The reaction mixture was stirred during two hours, followed by addition of water and extraction with dichloromethane. 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 CHCl₃-4-position of isoxazoline ring

($\delta=5.19$ ppm), and naphthalene ring ($\delta=4.53$ ppm, d, $J=6.5$ Hz, $\delta=6.24$ ppm, dd, $J=9.0$ and 6.5 Hz, $\delta=6.74$ 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 $\delta=67.9$ (C-4), 94.9 (C-5) and 151.5 ppm (C-3), and naphthalene ring moiety at $\delta=44.9$ (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 ^1H resonance of H-2' and H-8' methine ($\delta=6.84$ ppm) of naphthalene ring.

Scheme 1 Formation of Spiroisoxazolines(2)



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

* determined by ^1H nmr in the crude product.

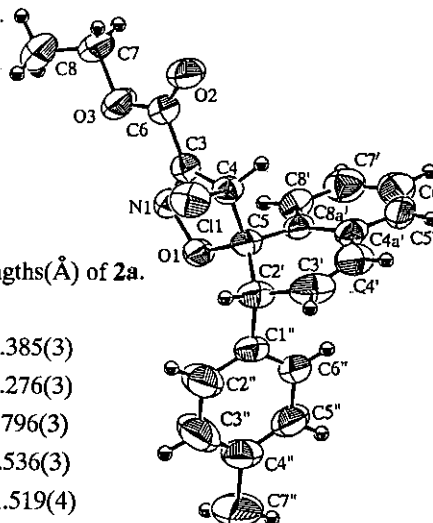


Table 1 Selected Torsional Angles(ϕ°) and Bond Lengths(\AA) of 2a.

| ($1/\phi^\circ$) | ($1/\text{\AA}$) |
|-----------------------------|--------------------|
| 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

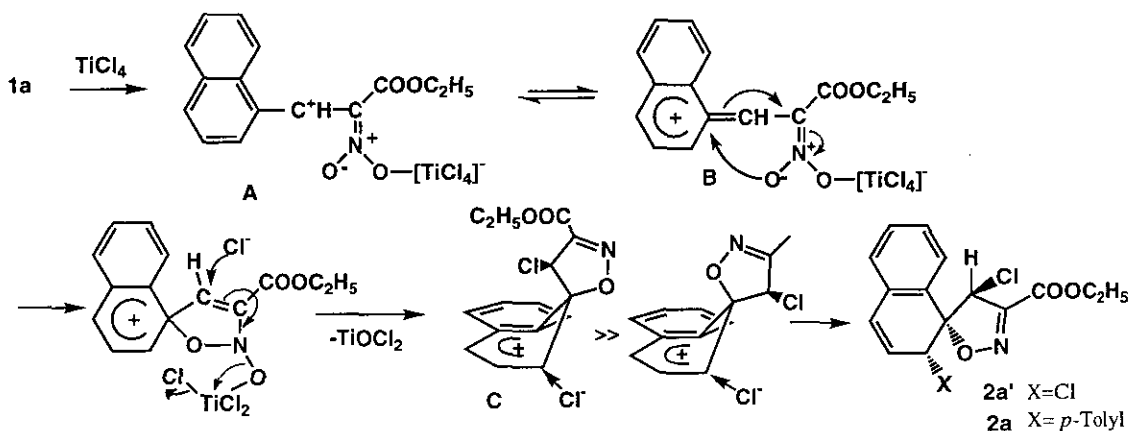
The structure of **2a**, in particular, the stereochemistry of 4- and 2'-positions was determined by single crystal X-ray analysis⁸. Thus, the relative structure of **2a** was determined to (*R*^{*})-4-chloro-3-ethoxycarbonyl-2'-tolylspiro [isoxazole-5(4*H*),1'(2'*H*)naphthalene], illustrated in Figure 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 ($\text{X}=\text{phenyl}$)¹⁰ and 2'-chlorinated spiroisoxazoline ($\text{X}=\text{Cl}$, **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'** ($\text{X}=\text{Cl}$) 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.

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

Scheme 2 A Proposed Reaction 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'-naphthyl)-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. Hirotsu and S. Zen, *Nippon Kagaku Kaishi*, **1993**, 948.
- 3 S. Hirotsu 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 $\text{C}_{22}\text{H}_{20}\text{NO}_3\text{Cl}$: 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(CH₂Cl₂-CH₃OH), ¹H and ¹³C nmr(CDCl₃, 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(CH₂Cl₂-CH₃OH), δ 4.58 and 45.8, 5.22 and 67.6, **2c':** 179.0–180.0°C(acetone-CH₃OH), δ 5.34 and 55.0, 5.11 and 65.6, **2d:** mp 71.0–73.0°C(ether-CH₃OH), 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(CH₂Cl₂-CH₃OH), 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**: C₂₂H₂₀NO₃Cl, MW=381.86, triclinic, space group *P*1, μ for Cu Kα=18.91 cm⁻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) Å³, Z=2, D_{calc}=1.284 g cm⁻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 MITHRIL⁹⁾ 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(CH₂Cl₂-CH₃OH), ¹H and ¹³C nmr(CDCl₃, 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 ¹³C nmr(CDCl₃, 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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