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Syntheses of substituted isoxazolines using Vilsmeier–Haack reagent

MURUGAPILLAI VENUGOPAL and
PARAMASIVAM T PERUMAL*
Organic Chemistry Division, Central Leather Research Institute, Adyar, Madras 600020, India

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Abstract. A new and short route for synthesis of substituted isoxazolines from 1-phenyl-3-hydroxylamino-3-(4-substituted phenyl) propan-1-one on reaction with phosphorus oxychloride and dimethyl formamide has been reported.

Keywords. Isoxazolines; propan-1-one derivatives; biologically active substances.

1. Introduction

Nitrogen-containing molecules possessing optical activity occupy a dominant position in the field of biologically active substances (Ariens *et al* 1983). It is reported that isoxazoline derivatives are of great interest to synthetic as well as pharmaceutical organic chemists. Isoxazolines also possess antimicrobial (Thakar and Bhawal 1977), fungicidal (Eckhard *et al* 1973), analgesic (Carr *et al* 1977; Nagano *et al* 1979), and diuretic (Ito and Saijo 1975) properties. As part of drug discovery, Wentland *et al* (1991) prepared a novel series of isoxazolo [4,5-*f*][3] benzazonine and isoxazolo [4,5-*g*][3]benzazecine derivatives that are analogues of the hypotensive dibenzazonine alkaloid protostephanene. Recent reports indicate that isoxazoline derivatives have received a lot of attention and are being prepared by different methods. We approached the synthesis of substituted isoxazolines through the Vilsmeier reagent.

The Vilsmeier–Haack–Arnold reaction (Jutz 1976) is a valuable means of introducing a formyl group into an activated aromatic ring. The chloromethyleniminium species (Vilsmeier reagent) can undergo attack by various carbon-nucleophiles. Recently, this reagent has been used to synthesise a variety of heterocyclic compounds (Bartmann *et al* 1988). It has also been used for cyclization reactions containing heteroatoms like sulphur, nitrogen and oxygen (Guzman and Romero 1990; Guzman *et al* 1990; Giles and Marson 1991), leading to five- and six-membered rings. Under Vilsmeier conditions, 2-hydroxyacetanilides or 2-hydroxyacetophenone oximes are efficiently transformed into benzoxazoles (Jayanth *et al* 1973). Oxazoles were synthesised from hippuric acid by treating with N-methylformanilide and phosphorus oxychloride (Cornforth 1953). In the presence of thionylchloride, dialkylformamides convert 6-aminouracil to isothiazolo-uracil (Furukawa *et al* 1976).

* For correspondence

Our studies with the Vilsmeier reaction on benzalacetone with different substituents on the aryl ring, at different temperatures, led to chloroformylated and arylformylated (or) only chloroformylated products, depending upon the temperature and the position of substitution in the aryl ring (Venugopal and Perumal 1991). Recently, we reported the conversion of a variety of substituted chalcones to the corresponding chlorindenes with excess of phosphorus oxychloride and dimethylformamide (Venugopal and Perumal 1991), and we synthesised substituted 5,6,7,8-tetrahydro-4H-1-benzopyran and 4H-pyran from the corresponding substituted 1,5,-diketones by use of the Vilsmeier reagent (Venugopal *et al* 1991).

Earlier, isoxazolines were synthesised by reaction of phenylchloroxime and alkenes with *bis*(tributyltin) oxide, which proceeded efficiently to give isoxazoline in moderate yields (Moriya *et al* 1991). Isoxazolines were also synthesised from hydroxylamino uracil reacting with Vilsmeier reagent (Nishiyaki *et al* 1978).

2. Results and discussion

In continuation of our studies, we wish to report here the synthesis of substituted isoxazolines from 1-phenyl-3hydroxylamino-3-(4-substituted phenyl)-propan-1-one. The results are summarized in table 1. Various hydroxylamine compounds (2) were synthesised from the chalcone (1) with hydroxylamine hydrochloride in the ratio 1:2 in the presence of sodium acetate. When chalcone was treated with hydroxylamine hydrochloride without sodium acetate, (2) was not obtained (see table 2).

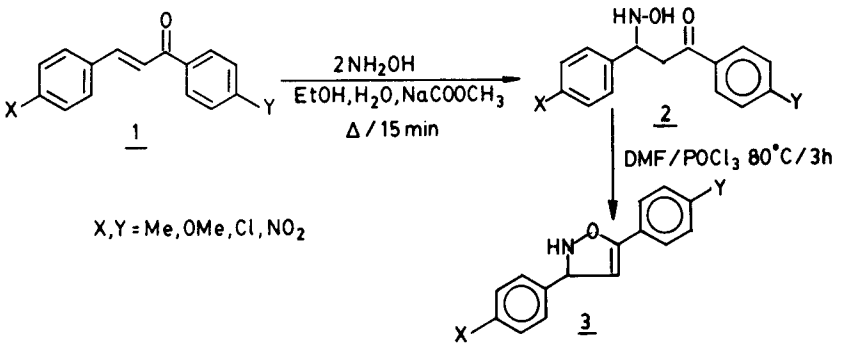
Table 1. Preparation of isoxazolines (3).

Compound	Substituents X	Substituents Y	Reaction temperature (°C)	Yield (%)
3a	H	H	80	25
3b	CH_3	H	80	40
3c	OCH_3	H	80	42
3d	Cl	H	0	40
3e	NO_2	H	0	43
3f	H	OCH_3	0	50

This refers to the section where the compound preparation and characters are given.

Table 2. Preparation of 2.

Compound	X	Y	Yield (%)
2a	H	H	55
2b	CH_3	H	50
2c	OCH_3	H	52
2d	Cl	H	48
2e	NO_3	H	65
2f	H	OCH_3	58



Scheme 1.

During the course of reaction, (2) was transformed into its enol form and it was cyclized by Vilsmeier reagent as follows. Compound (2) in methylene chloride was added dropwise to Vilsmeier reagent ($DMF/POCl_3$) at 0–5°C. After completion of the addition, the reaction mixture was stirred for 3h at room temperature and then decomposed in water and worked up. In some cases, it was heated at 80°C for 3 h. On being heated above 100°C, the material was polymerized. This is the first time substituted isoxazolines have been prepared using Vilsmeier reagent.

3. Experimental

3.1 *Preparation of 3,5-diphenylisoxazolines – general procedure*

To dimethylformamide (5 ml) at 0°C. phosphorus oxychloride (3 ml) was added dropwise with stirring. The reaction mixture was left at room temperature for 1 h and then a solution of substituted hydroxylamine in anhydrous dichloromethane (10 ml) was added and the resulting reaction mixture was stirred for 2 h at room temperature. After addition, the reaction mixture was heated at 80°C for 3 h. This was then cooled to room temperature and poured into ice cold water containing sodium acetate. After the usual work up and purification by column chromatography on silica gel (60–120) mesh) using petroleum ether: chloroform as eluent, the isoxazolines were obtained.

3.2 *3,5-Diphenyl isoxazoline*

1,3-Diphenyl-3-hydroxylamino propan-1-one (2·5 g, 10 mmol), was treated with Vilsmeier reagent according to the general procedure described. The crude product isolated was passed through a column of silica gel. Elution with petroleum ether and chloroform (8:2) gave compound 3a (0·58 g, 25% yield). White solid, m.p. 152°C. IR: 3276 cm^{-1} (N–H), 950 cm^{-1} (–N–O), 900 cm^{-1} (C–O–N in 5-membered ring); ^1H NMR ($CDCl_3$ + DMSO-d_6) 6·64–6·8 (1H, *d*) 7·01–7·77 (11H, *m*, aromatic) 7·96 (1H, broad singlet, NH proton). Analysis – calculated for $C_{15}H_{12}NO$: C, 80·71; H, 5·83%. Found: C, 80·92; H, 5·75%.

3.3 *3-(4-Methylphenyl)-5-phenyl isoxazoline*

1-Phenyl-3hydroxylamino-3-(4-methylphenyl) propan-1-one (2·6 g 10 mmol) was treated with Vilsmeier reagent according to the general procedure. The crude product

isolated was passed through a column of silica gel. Elution with petroleum ether and chloroform (7:3) gave 3b (0·95 g, 40% yield). White solid, m.p. 168°C. IR: 3275 cm^{-1} (N–H), 948 cm^{-1} (N–O), 903 cm^{-1} (C–O–N in 5-membered ring); ^1H NMR ($CDCl_3$ + DMSO-d_6) 2·34–6·8 (3H, *s*, Ar–CH_3), 6·43–6·6 (1H, *d*) 7·08–7·79 (11H, *m*, aromatic and one NH proton). MS (*M/z*): 237, 145, 115, 91. Analysis – calculated for ($C_{16}H_{15}NO$): C, 81·01; H, 6·33%. Found: C, 79·85; H, 6·48%.

3.4 *3-(-Methoxylphenyl)-5-phenyl isoxazoline*

1-Phenyl-3-hydroxylamino-3-(4-chlorophenyl) propan-1-one (2·9 g, 10 mmol) was treated with Vilsmeier reagent according to the general procedure. The crude product isolated was passed through a column of silica gel. Elution with petroleum ether and chloroform (4:6) gave 3c (1·07 g, 40% yield). White solid, m.p. 175°C. IR: 3275 cm^{-1} (N–H), 945 cm^{-1} (C–O–N in 5-membered ring); ^1H NMR ($CDCl_3$ + DMSO-d_6) 6·8–6·97 (1H, *d*, N–CH–C=), 7·10–7·60 (10 H, *m*, aromatic and one olefinic proton). Analysis – calculated for $C_{16}H_{15}NO_2$: C, 75·89; H, 5·93%. Found: C, 76·21; H, 6·05%.

3.5 *3-(4-Chlorophenyl)-5-phenyl isoxazoline*

1-Phenyl-3-hydroxylamine-3-(4-chlorophenyl) propan-1-one (2·8 g, 10 mmol) and Vilsmeier reagent were reacted as per the general procedure. The crude product isolated was passed through a column of silica gel. Elution with petroleum ether and chloroform (4:6) gave 3d (1·07 g, 40% yield). White solid, m.p. 175°C. IR: 3275 cm^{-1} (N–H), 945 cm^{-1} (–N–O), 902 cm^{-1} (C–O–N in 5-membered ring); ^1H NMR ($CDCl_3$ + DMSO-d_6) 6·8–6·97 (1H, *d*, N–CH–C=), 7·10–7·60 (10H, *m*, aromatic protons and one olefinic proton). Analysis – calculated for $C_{16}H_{12}ClNO$: C, 67·05; H, 4·47%. Found: C, 67·81; H, 4·32%.

3.6 *3-(4-Nitrophenyl)-5-phenyl isoxazoline*

1-Phenyl-3-hydroxylamino-3-(4-nitrophenyl) propan-1-one (2·9 g, 10 mmol) was treated with Vilsmeier reagent as per the general procedure. The crude product isolated was passed through a column of silica gel. Elution with petroleum ether and chloroform (3:7) gave 3e (1·15 g, 43% yield). Brown solid, m.p. 171°C. IR: 3268 cm^{-1} (N–H), 940 cm^{-1} (–N–O), 900 cm^{-1} (C–O–N in 5-membered ring); ^1H NMR ($CDCl_3$ + DMSO-d_6) 6·48–6·64 (1H, *d*, –NH–CH–C=), 7·06–8·21 (10H, *m*, aromatic protons and one olefinic proton), 8·01 (1H broad singlet, –NH proton). Analysis – calculated for $C_{15}H_{12}N_2O_3$: C, 67·16; H, 4·48%. Found: C, 67·56; H, 4·22%.

3.7 *3-Phenyl-5-(4-methoxyphenyl)-isoxazoline*

1-(4-Methoxyphenyl)-3-hydroxylamino-3-phenyl propan-1-one (2·75 g, 10 mmol) was subjected to Vilsmeier reaction according to the general procedure. The crude product isolated was passed through a column of silica gel. Elution with petroleum ether and chloroform (60:40) gave 3f (1·09 g, 43% yield). White solid, m.p. 162°C. IR: 3272 cm^{-1} (N–H), 945 cm^{-1} (–N–O), 900 cm^{-1} (C–O–N in 5-membered ring); ^1H NMR ($CDCl_3$ + DMSO-d_6): 3·79–3·79 (3H, *s*, ArOCH_3), 6·46–6·51 (1H, *d*), 6·8–6·83 (2H, *d*, aromatic), 7·09–7·7 (8H, aromatic proton and one olefinic proton), 7·98

(1H, broad singlet, –NH proton). ^{13}C NMR: 55·2, 114·8, 117·2, 119, 124·5, 127·4, 129, 129·6, 138·2, 141·9, 167·8. MS (*M/z*): 253 (20), 131 (90), 123 (100% base peak), 103 (50, 77, 40). Analysis – calculated for $C_{16}H_{15}NO$: C, 75·89; H, 5·93%. Found: C, 75·52; H, 5·84%.

References

Ariens E J, Soudijn W and Timmermans P B M W M 1983 *Stereochemistry, and biological activity of drugs* (Oxford: Blackwell Scientific)
Bartmann W, Konz E and Ruger W 1988 *Synthesis* **9** 680
Cornforth J W 1953 *Heterocycl. Conf.* **5** 346
Eckhard I F, Lehtonen K, Staub T and Summers L A 1973 *Aust. J. Chem.* **26** 2705
Carr J B, Durham H G and Hass D K 1977 *J. Med. Chem.* **20** 934
Furukawa Y, Miyershita O and Shima S 1976 *Chem. Pharm. Bull.* **24** 970
Giles P R and Marson M 1991 *Tetrahedron* **47** 1303
Guzman A, Romero M and Muchowski 1990 *Can. J. Chem.* **68** 791
Guzman A and Romero M 1990 *J. Org. Chem.* **55** 5493
Ito N and Saijo S 1975 *Jpn. Kokai* 7595272
Jayanth M R, Naik H A, Tatke D R and Seshadri S 1973 *Indian J. Chem.* **11** 1112
Jutz C 1976 *Adv. Org.* (New York: Wiley Interscience) **9** 225
Moriya O, Urata Y and Endo T 1991 *Chem. Commun.* **17**
Nagano M, Sakai J, Mizukai M, Makamura N, Misaka E, Kobayashi S and Tomita K 1979 *Jpn. Kokai* 7973774
Nishiyaki S, Kanamori Y and Senga K 1978 *Chem. Pharm. Bull.* **26** 2497
Thakar K A and Bhawal B M 1977 *J. Indian Chem. Soc.* **54** 875
Venugopal M and Perumal P T 1991 *Org. Prep. Proc. Int.* **23** 749
Venugopal M and Perumal P T 1991 *Synth. Commun.* **21** 515
Venugopal M, Umarani R, Perumal P T and Rajadurai S 1991 *Tetrahedron Lett.* **32** 3235
Wentland M P, Kullnig R K and Tham F S 1991 *J. Org. Chem.* **56** 4701