The Preparation of Arylpropiolic Acids *via* Styrylisoxazoles

S. Chimichi, F. De Sio, D. Donati, R. Pepino, L. Rabatti and P. Sarti-Fantoni*

Centro di studio del C.N.R. sulla chimica e la struttura dei composti eterociclici e loro applicazioni, c/o Istituto di Chimica Organica dell'Universitá, Via G. Capponi, 9, Firenze, Italia

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The *vic*-dibromo derivatives obtained by bromine addition to 3-methyl-4-nitro-5-styrylisoxazoles were used as starting materials for the preparation of arylpropiolic acids.

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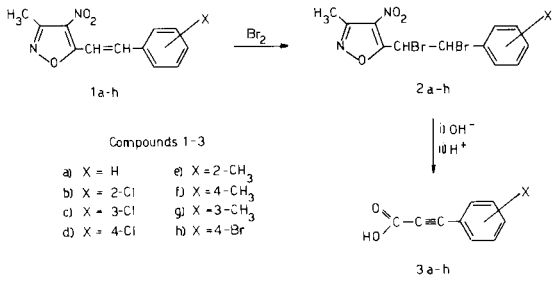
Many heterocyclic compounds have been prepared recently and used for protecting functional groups during the synthesis of organic compounds (1,2). As an example, oxazolines (2) were used for masking the carboxyl group, whereas the requisite isoxazole derivatives were considered as intermediate for the preparation of β-diketones (3), α,β-unsaturated ketones (4), 1,4-diketones (5) and β-aminoenones (3,4). In a previous study (6) the preparation of *trans*-cinnamic acids *via* 3-methyl-4-nitro-5-styrylisoxazoles was reported. In fact the alkaline hydrolysis of these compounds, followed by acidification, led to the expected acids. In addition, the mechanism of the alkaline isoxazole ring opening was investigated and clarified by using $Na^{18}OH$ (7). Because the above results suggested that the 3-methyl-4-nitroisoxazol-5-yl group may be considered as a masked carboxyl group, we have prepared a series of 3-methyl-4-nitro-5-styrylisoxazoles **1a-h** in order to obtain arylpropiolic acids **3a-h** *via* 5-(1,2-dibromo-2-phenylethyl)-3-methyl-4-nitroisoxazoles **2a-h**. These compounds were prepared by extending the procedure described by Quilico and Musante (8), concerning the addition of bromine to 3-methyl-4-nitro-5-styrylisoxazole (**1a**). The *vic*-dibromo derivatives **2a-h** (see Table 1) were then used to give arylpropiolic acids **3a-h**, as reported in the following scheme.

Scheme



Alkaline hydrolysis of the dibromo derivatives followed by acidification leading to arylpropiolic acids were performed according to the procedure already described for the preparation of cinnamic acids *via* 3-methyl-4-nitro-5-styrylisoxazoles (6). The melting points reported in Table 2 for the acids **3a-h** obtained with the above route are in good agreement with those reported in the literature for the corresponding arylpropiolic acids. Because the high yields of 3-methyl-4-nitro-5-styrylisoxazoles prepared by condensation reaction of aromatic aldehydes with 3,5-dimethyl-4-nitroisoxazole, the above described method is a good route to obtain arylpropiolic acids with two more carbon atoms with respect to the aromatic aldehydes used. *Trans* structure for compounds **1a-f** were based both on ^3J of olefinic protons (15-16 Hz) in the nmr spectra and on the *trans* structure of the cinnamic acids obtained by hydrolysis (6). For compounds **1g-h**, the same spectroscopic considerations apply.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 283 spectrophotometer. The ir spectral data are recorded in reciprocal centimeters (cm^{-1}). The ^1H nmr spectra were obtained on a Perkin-Elmer R 32 spectrometer. Chemical shifts are reported in ppm from TMS as internal standard and are given in δ units. The uv spectra were determined on a Cary 14 spectrophotometer.

3-Methyl-4-nitro-5-styrylisoxazoles (**1a-f**).

Compounds **1a-f**, prepared according to the general procedure (9), showed mps in agreement with those already reported in the references (6,10,11). The yields were the following: **1a** = 93%, lit 96% (9), **1b**, = 54%, **1c** = 74%, **1d** = 90%, **1e** = 85%, **1f** = 80%.

3-Methyl-4-nitro-5-(3-methylstyryl)isoxazole (**1g**).

This compound, prepared as described in reference (9) for **1a**, had mp 143-144° (from ethanol, yield 93%); ir (potassium bromide): 1625, 1570, 1500, 1360, 1190, 965 and 780 cm^{-1}; uv (methanol): λ max, nm (log ε) 250 sh (3.98), 268 (4.02), 360 (4.19); nmr (deuteriochloroform): 2.38 (s, 3H, *m*-CH_3), 2.55 (s, 3H, 3-CH_3), 7.35 (m, 4H), 7.53 (d, 1H, 16 Hz), 7.80 (d, 1H, 16 Hz).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.00; H, 4.89; N, 11.44.

3-Methyl-4-nitro-5-(4-bromostyryl)isoxazole (**1h**).

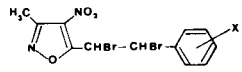
This compound, prepared as described in reference (9) for **1a**, had mp 188-190° (from ethanol, yield 79%); ir (potassium bromide): 1620, 1575, 1505, 1380, 1355, 1145 and 820 cm^{-1}; uv (methanol): λ max, nm (log ε) 245 (4.08), 268 (4.15), 357 (4.40); nmr (deuteriochloroform): 2.58 (s, 3H), 7.45 (d, 1H, 15 Hz), 7.50 (m, 4H), 7.70 (d, 1H, 15 Hz).

Anal. Calcd. for $C_{12}H_9BrN_2O_3$: C, 46.52; H, 2.90; N, 9.05. Found: C, 46.34; H, 2.91; N, 9.21.

5-(1,2-Dibromo-2-phenylethyl)-3-methyl-4-nitroisoxazoles (**2a-h**).

According to the literature (8), compound **2a** was obtained by treating a solution of **1a** (2.24 g) in carbon disulphide (100 ml) with bromine (0.5

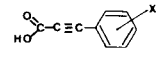
Table 1



Compound	X	Yield %	Mp °C	Formula	Analysis Calcd. (Found) C	H	N	Chemical Shift (deuteriochloroform)
2a	H	73	167-168 (8) 171 (10)	$C_{12}H_{10}Br_2N_2O_3$				2.62 (s, 3H, CH_3), 5.62 (d, 1H), 6.36 (d, 1H), 7.50 (m, 5H)
2b	2-Cl	98	127-130 (a)	$C_{12}H_9Br_2ClN_2O_3$	33.93 (33.95	2.12 2.14	6.59 6.63)	2.65 (s, 3H, CH_3), 6.36 (AB system, 2H), 7.30-7.80 (m, 4H)
2c	3-Cl	99	166-168 (b)	$C_{12}H_9Br_2ClN_2O_3$	33.93 (33.70	2.12 2.00	6.59 6.42)	2.62 (s, 3H, CH_3), 5.57 (d, 1H), 6.30 (d, 1H), 7.30-7.60 (m, 4H)
2d	4-Cl	95	168-170 (a)	$C_{12}H_9Br_2ClN_2O_3$	33.93 (34.17	2.12 2.24	6.59 6.65)	2.65 (s, 3H, CH_3), 5.58 (d, 1H), 6.30 (d, 1H), 7.46 (s, 4H)
2e	2-CH_3	97	151-153 (b)	$C_{13}H_{12}Br_2N_2O_3$	38.61 (38.83	2.97 3.00	6.93 6.84)	2.50 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 5.94 (d, 1H), 6.45 (d, 1H), 7.15-7.70 (m, 4H)
2f	4-CH_3	82	173-175 (a)	$C_{13}H_{12}Br_2N_2O_3$	38.61 (38.72	2.97 3.12	6.93 7.03)	2.32 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 5.59 (d, 1H), 6.37 (d, 1H), 7.15-7.60 (m, 4H)
2g	3-CH_3	98	154-155 (b)	$C_{13}H_{12}Br_2N_2O_3$	38.61 (38.41	2.97 2.83	6.93 7.01)	2.40 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 5.80 (d, 1H), 6.90 (d, 1H), 7.32 (m, 4H)
2h	4-Br	95	175-176 (b)	$C_{12}H_9Br_3N_2O_3$	30.70 (30.98	1.92 1.99	5.97 6.19)	2.61 (s, 3H, CH_3), 5.55 (d, 1H), 6.29 (d, 1H), 7.30-7.70 (m, 4H)

Recrystallized from: (a) ethanol, (b) carbon tetrachloride.

Table 2



Compound	X	Yield %	Mp °C Found	Mp °C Lit	IR, ν max cm^{-1} C≡C	IR, ν max cm^{-1} C=O
3a	H	48.2	134-135	135 (12)	2240-2200	1680
3b	2-Cl	47.6	130-131	131-132 (12)	2220	1700
3c	3-Cl	30.6	140-141	140-141 (12)	2210	1690
3d	4-Cl	54.0	191-193	192-194 (12)	2230-2205	1695
3e	2-CH_3	49.5	90-91	94-95 (13)	2210-1195	1695
3f	4-CH_3	72.0	147-148	148 (14)	2230-2195	1675
3g	3-CH_3	34.0	124-126	109.5 (15)	2210	1680
3h	4-Br	78.6	200-201	201-202 (12)	2230-2200	1695

ml). The solution was then stirred at room temperature for two hours. Evaporation of the solvent left a colourless product (2.77 g), mp 167-168° (from ethanol), lit 167-168° (8), 171° (10). The same procedure was used for the preparation of dibromo derivatives **2b-h**. Yields, mps, elemental analysis and chemical shifts are reported in Table 1.

Arylpropiolic Acids (**3a-h**).

Compound **2a** (1.5 g) suspended in aqueous 1 *N* sodium hydroxide (30 ml), was refluxed (10 hours) to give the corresponding phenylpropiolate. Small amount of unreacted dibromo derivative was then filtered off and the yellow solution, acidified with concentrated hydrochloric acid until the *p*H was 1, gave a solid product which was filtered (0.27 g, 48%), mp 134-135° (carbon tetrachloride), lit 135° (12). The infrared spectra of the product and the authentic material were identical. The same procedure was used for the preparation of arylpropiolic acids **3b-h**. Mps, yields and ir frequencies are reported in Table 2.

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