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Regioselective synthesis and side-chain metallation and elaboration of 3-aryl-5-alkylisoxazoles

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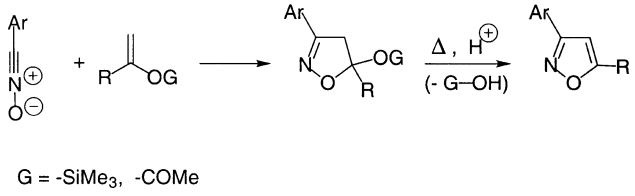
Abstract—A number of 3-aryl-5-alkylisoxazoles have been synthesized in high yields by reacting arylnitrile oxides with free enolate ions regioselectively obtained by metallation of various alkyl methyl ketones with LDA in THF at −78°C followed by dehydration. Investigations concerning regioselective side-chain metallation and elaboration of one of them (3-phenyl-5-ethylisoxazole) have also been carried out.

Isoxazoles are well-known systems, interesting from several points of view,[1] including their use in organic synthesis. Among other things, versatile difunctionalized derivatives (1,3-dicarbonyl or 1,3-iminocarbonyl) can in fact be obtained by ring opening of such systems (N–O bond cleavage),[2] so that isoxazoles can be considered useful masked forms of those compounds. In this perspective the availability of a wide number of variously substituted isoxazoles enhances their synthetic potential, allowing the synthesis of more complex (and/or further functionalized) dicarbonyl (or iminocarbonyl) derivatives.

In this context 3-aryl-5-alkylisoxazoles are particularly interesting if one considers the large number of potential elaborations (via α-metallation of the side-chain and subsequent quenching with various electrophiles) which allow their transformation into numerous other isoxazole derivatives.

On the other hand, concerning the synthesis of 3-aryl-5-alkylisoxazoles themselves, various synthetic procedures have so far been proposed.[3] Two of them, in particular, utilize the 1,3-dipolar addition of arylnitrile oxides to stable enolate derivatives (silyl enol ethers[4] or enol acetates[5]) followed by final aromatization of the formed isoxazolines (Scheme 1).

The overall yields reported for such procedures are, however, moderate or low (4–46 and 28% for silyl enol ethers and enol acetates, respectively). Much better results were instead observed by us in the synthesis of 4,5-unsubstituted-3-arylisoxazoles by the analogous 1,3-dipolar addition of aryl nitrile oxides to the 'free' enolate ion of acetaldehyde



Scheme 1.

(quantitatively generated by the known cycloreversion of THF in the presence of *n*-BuLi at room temperature),[6] in which case high yields of both 3-aryl-5-hydroxy-2-isoxazolines and, from these, the corresponding 3-arylisoxazoles were obtained.[7]

This suggested that better results could be obtained even in the synthesis of 3-aryl-5-alkyl-5-hydroxy-2-isoxazolines (and so also of 3-aryl-5-alkylisoxazoles) simply by using directly the proper enolate ions (regioselectively generated from methyl ketones) instead of the corresponding silyl enol ethers or enol acetates.

Thus, we treated a number of methyl ketones with LDA in THF at −78°C (well-known conditions[8] favouring proton abstraction from the methyl group: [A] in Scheme 2), actually obtaining by subsequent reaction with various arylnitrile oxides, high yields of the expected 3-aryl-5-hydroxy-2-isoxazolines in all cases (Table 1). The phenylnitrile oxide reacted smoothly with the enolates in a ratio 1:1.2, whereas the other arylnitrile oxides gave a cleaner reaction only by using a higher amount of enolate was used (Table 1).

After separation, 5-hydroxyisoxazolines **1** were subjected to dehydration/aromatization in basic conditions analogous to those reported by us for 3-aryl-5-hydroxy-2-isoxazolines,[7]

Keywords: isoxazolines; isoxazoles; synthesis; metallation.
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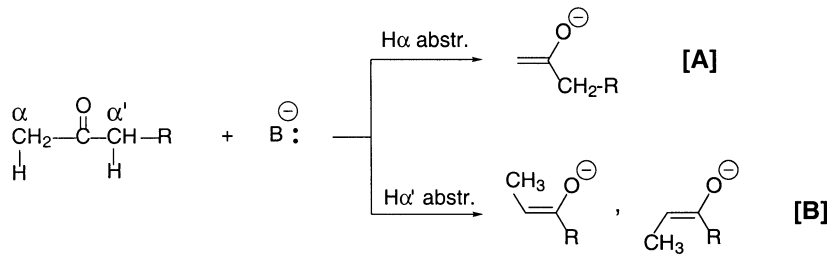
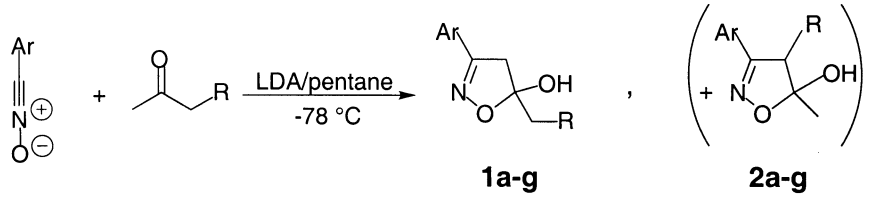


Scheme 2.

Table 1. Yields of 3-aryl-5-alkyl-5-hydroxy-2-isoxazolines **1** isolated from the reaction of arylnitrile oxides and ketones in the presence of LDA

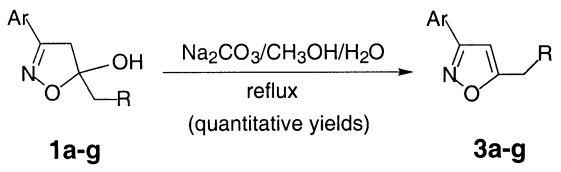


Entry	Ar	R	Enolate/nitrile oxide	Yield of **1** (and **3**) (%)[a]	Regioselection (**1/2**)[b]
1a	C_6H_5	Me	1.2:1	74	92:8
1b	C_6H_5	Et	1.2:1	70	89:11
1c	C_6H_5	*n*-Bu	1.2:1	76	93:7
1d	C_6H_5	Benzyl	1.2:1	71	91:9
1e	2-Cl–C_6H_4	Me	5:1	83	92:8
1f	3-NO_2–C_6H_4	Me	5:1	70	94:6
1g	Mesityl	Me	3:1	82	92:8

[a] Values refer to the 5-hydroxyisoxazolines actually isolated by chromatography.
[b] Regioselectivity ratio (**1/2**) was evaluated by GC.

affording in quantitative yields the corresponding 3-aryl-5-alkylisoxazoles **3** (Table 1 and Scheme 3). Regioselectivity ratio (**1/2**) was determined by GC. The minor isomers **2** were not isolated due to the rather small quantities formed (5–9%). Their formation was detected by GC–MS analysis as the two isomers **1** and **2** have quite distinct mass spectra (see Section 1).

Side-chain metallation and elaboration of one of the so synthesized isoxazoles (i.e. 3-phenyl-5-ethylisoxazole) was then investigated. Concerning the metallation, alkyllithiums (*n*-BuLi, *t*-BuLi) at −78°C were the first bases tried. Previous reports[9] on the metallation with *n*-BuLi of some 5-methylisoxazoles (3,5-dimethylisoxazole, 3-phenyl-5-methylisoxazole) indicated proton abstraction from the C_5 methyl group as the only observed reaction. Both systems, in fact, by reaction with *n*-BuLi followed by treatment with CO_2, afforded the corresponding isoxazole-5-acetic acid (3-methylisoxazole-, and 3-phenylisoxazole-5-acetic acid, respectively). A different behaviour was instead described for 5-methylisoxazoles bearing a group containing a heteroatom (e.g. OMe group) in the 3-position.[10] In these cases, in fact, probably due to the presence of such a heteroatom, the lithium cation of the alkyllithium can competitively interact with either the endocyclic oxygen or with the exocyclic heteroatom, so bringing in part the base also close to C_4-proton of the isoxazole. Possibly due to this situation, in the latter case C_4-proton metallation was observed in competition with that at the C_5–Me. In any case, the use of a base capable of co-ordinating the lithium cation (e.g. LDA), by lowering the importance of the above-mentioned interactions, suppressed such a competition affording only metallation at the more acidic site (C_5–Me: conjugate base stabilized by resonance).[11]



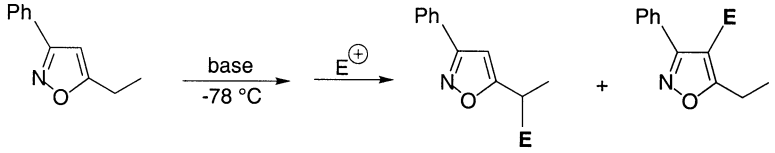
Scheme 3.

However, when the alkyl group on C_5 is more complex than Me group, due to the fact that metallation at Cα position becomes more difficult (for electronic, statistical, and steric reasons) competition by C_3–Me hydrogens has also been observed under kinetically controlled conditions (reactions of some 3-methyl-5-alkylisoxazoles with alkyllithiums).[12]

α-Metallation at the C_5 alkyl group is again the preferred reaction when an alkyl group with the same features is present on both positions (e.g. in the case of 3,5-diethyl-4-methylisoxazole).[13]

In our case, since the 'protecting' group on C_3 lacks a suitable heteroatom (so not favouring C_4-proton competitive abstraction) as well as α-hydrogens (being thus unable to compete itself as for the proton-abstraction), clean metallation at the α-position of C_5-ethyl group could then have been expected.

Table 2. Side-chain metallation and elaboration of 3-phenyl-5-ethylisoxazole



4a, b **5**

Base	Substrate/base ratio	Electrophile	Substrate/electrophile ratio	Products (yield %)[a]	**4/5** ratio[b]
n-BuLi	1:1.2	CH_3I	1:10	**4a** (40)[b], **5** (14)[b]	3:1
t-BuLi	1:1.2	CH_3I	1:10	**4a** (32)[b], **5** (8)[b]	4:1
LDA	1:1.5	CH_3I	1:10	**4a** (78)	–
LDA	1:1.5	$PhCH_2Br$	1:1.5	**4b** (81)[c]	–
LTMP	1:1.5	CH_3I	1:10	**4a** (97)	–

[a] Unless otherwise indicated values refer to isolated products by silica gel chromatography.
[b] Values determined by GC analysis.
[c] Up to 12% of 1-bromo-1,2-diphenylethene were also observed.

Quenching of the metallation product with electrophiles indicates instead that *n*-BuLi (and to a less extent *t*-BuLi) causes the metallation also at the 4-position of isoxazoles (Table 2).

This unexpected result is possibly due to the minor relative acidity of Cα-proton (in our case of an ethyl instead of methyl group) as well as to the great basicity of alkyllithiums (lowering the selectivity), and seems to be somewhat attenuated in the case of *t*-BuLi (in spite of its even greater basicity compared to *n*-BuLi)[14] possibly because of steric reasons presumably affecting C_4-proton abstraction to a more extent with respect to the side chain Cα-proton.

According to this hypothesis, the use of lithium amides (LDA, LTMP), much less basic compared to alkyllithiums as well as also sterically hindered (especially LTMP), completely suppresses the competition. Alternative explanations concerning the observed behaviour of lithium amides (e.g. attributing it to their co-ordinating ability towards lithium cation as previously proposed)[11] seem in fact to be rather unlikely in our case because of the absence of a group providing a heteroatom on the 3-position of the isoxazole.

In conclusion, the present investigation has established conditions for the regioselective accomplishment in high yields not only of the synthesis of 3-aryl-5-alkylisoxazoles, but also of side-chain metallation and elaboration of one of them, that is one with a relatively complex side-chain (compared to a Me group). Further investigations are now in progress aimed to verify the possibility of extending the above results also to the metallation/elaboration of other 3-aryl-5-alkylisoxazoles, as well as to make stereoselective elaborations.

1. Experimental

1.1. General methods

Melting points taken on Electrothermal apparatus were uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on a Varian EM 390 or Mercury 300 MHz spectrometer and chemical shifts are reported in parts per million (δ). Absolute values of the coupling constant are reported. IR spectra were recorded on a Perkin–Elmer 681 spectrometer. GC analyses were performed by using a HP1 column (methyl silicone gum; 5 m×0.53 mm×2.65 μm film thickness) on an HP 5890 model, Series II. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator, the spots on the TLC were observed under ultraviolet light or were visualized with I_2 vapour. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 ASTM. GC–MS analyses were performed on an HP 5995C model and microanalyses on a Elemental Analyzer 1106—Carlo Erba-instrument.

1.2. Materials

Nitrile oxides were prepared in all cases from aldehydes through their conversion into the corresponding oximes and then into benzohydroximinoyl chlorides. These were finally converted into nitrile oxides by treatment with NEt_3. Pentane from commercial source was purified by distillation from CaH_2 under nitrogen. Tetrahydrofuran (THF) from commercial source was purified by distillation (twice) from sodium wire under nitrogen. Standardized (2.4 M) *n*-butyllithium in hexane (1.3 M) *sec*-butyllithium in cyclohexane and (1.7 M) *t*-butyllithium in pentane were purchased from Aldrich Chemical Co. Titration of *n*-butyllithium, *sec*-butyllithium and *t*-butyllithium were performed by using *N*-pivaloyl-*o*-toluidine.[15] All other chemicals and solvents were commercial grade further purified by distillation or crystallization prior to use.

1.3. Preparation of 3-aryl-5-ethyl-5-hydroxy-2-isoxazolines 1a–f by reaction of arylnitrile oxides with ketones (see Table 1): general procedure

A 1.3 M solution of *sec*-butyllithium in cyclohexane (5.18 mL, 7.8 mmol) was added to diisopropylamine (1.1 mL, 7.8 mmol) in pentane (10 mL) at 0°C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and three dropping funnels. After the mixture had been stirred for 20 min, the temperature was brought down to −78°C

and a solution of arylnitrile oxide (6.5 mmol) in pentane (75 mL) and a solution of the ketone (7.8 mmol) in pentane (25 mL) were simultaneously dropwise added. The yellow reaction mixture kept at −78°C was stirred for 2 h. Then, the reaction was quenched by adding water. The reaction products were extracted three times with ethyl acetate. The organic phase was dried with anhydrous Na_2SO_4 and then evaporated. Column chromatography (silica gel, petroleum ether/ethyl acetate=7:3) of the residue affords the 3-aryl-5-hydroxy-5-alkyl-2-isoxazoline in 70–83% yield.

A 2.4 M solution of *n*-butyllithium (32.5 mmol) in hexane was used to generate the diisopropylamide (LDA) (32.5 mmol) in the synthesis of isoxazolines involving the 2-chlorobenzonitrile oxide (7.8 mmol) or 3-nitrobenzonitrile oxide (7.8 mmol).

1.3.1. 3-Phenyl-5-ethyl-5-hydroxy-2-isoxazoline (1a). White crystals. 74% yield. Mp 72–74°C; IR (KBr): 3253, 2970, 1597, 1326, 1276, 1170, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.67–7.64 (2H, m, aromatic protons); 7.41–7.37 (3H, m, aromatic protons); 3.25 (2H, s); 2.69 (1H, bs, OH: exchange with D_2O); 2.02 (2H, q, J=7.4 Hz); 1.08 (3H, t, J=7.4 Hz). GC–MS (70 eV) *m/z* (rel. int.): 191 (M^+, 38), 174 (52), 173 (39), 162 (10), 146 (15), 144 (100), 135 (53), 134 (43), 117 (44), 116 (18), 103 (37), 77 (71), 51 (20). Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.81; N, 7.33. Found: C, 69.33; H, 7.10; N, 7.20.

1.3.2. 3-Phenyl-5-(*n*-propyl)-5-hydroxy-2-isoxazoline (1b). Colourless oil. 70% yield. IR (neat): 3375, 2962, 2900, 2874, 1597, 1497, 1361, 920, 850, 759, 692 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.73–7.58 (2H, m, aromatic protons); 7.50–7.35 (3H, m, aromatic protons); 3.28 (2H, s); 3.10–2.85 (1H, bs, OH: exchange with D_2O); 2.05–1.84 (2H, m); 1.65–1.39 (2H, m); 1.00 (3H, t, J=7.4 Hz). GC–MS (70 eV) *m/z* (rel. int.): 205 (M^+, 51), 189 (15), 188 (98), 187 (15), 162 (17), 144 (34), 135 (10), 134 (57), 120 (14), 118 (12), 117 (77), 103 (34), 91 (12), 77 (82), 71 (84), 51 (22), 43 (73), 41 (16). Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83. Found: C, 70.21; H, 7.38; N, 6.80.

1.3.3. 3-Phenyl-5-(*n*-pentyl)-5-hydroxy-2-isoxazoline (1c). Colourless oil. 76% yield. IR (neat): 3383, 3062, 2980, 2875, 2861, 1568, 1447, 1361, 1229, 1075, 919, 855, 759, 692 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.70–7.62 (2H, m, aromatic protons); 7.43–7.35 (3H, m, aromatic protons); 3.25 (2H, s); 2.78–2.70 (1H, bs, OH: exchange with D_2O); 2.00–1.91 (2H, m); 1.64–1.43 (4H, m); 1.41–1.28 (2H, m); 0.88 (3H, t, J=7.4 Hz). GC–MS (70 eV) *m/z* (rel. int.): 233 (M^+, 28), 217 (14), 216 (82), 215 (12), 162 (16), 159 (11), 144 (22), 135 (100), 120 (12), 118 (16), 117 (92), 103 (27), 99 (69), 91 (11), 77 (65), 71 (54), 51 (15), 43 (62), 41 (17). Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found: 72.18; H, 8.21; N, 6.00.

1.3.4. 3-Phenyl-5-(2-phenyl-1-ethyl)-5-hydroxy-2-isoxazoline (1d). White crystals. 71% yield. Mp 130–131°C; IR (KBr): 3512, 3040, 2932, 2980, 1601, 1495, 1446, 1357, 1235, 1097, 1065, 899, 852, 712 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.67–7.60 (2H, m, aromatic protons); 7.44–7.36 (3H, m, aromatic protons); 7.34–7.12 (5H, m, aromatic protons); 3.30–3.24 (1H, d, J=17.4 Hz); 3.23–3.18 (1H, d, J=17.4 Hz); 2.95–2.80 (2H, m); 2.40–2.22 (2H, m); 1.68–1.40 (1H, bs, OH: exchange with D_2O). GC–MS (70 eV) *m/z* (rel. int.): 267 (M^+, 14), 250 (33), 249 (32), 135 (24), 134 (12), 105 (58), 104 (14), 103 (15), 92 (89), 91 (100), 77 (27). Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37; N, 5.24. Found: C, 76.35; H, 6.31; N, 5.18.

1.3.5. 3-(2-Chlorophenyl)-5-ethyl-5-hydroxy-2-isoxazoline (1e). Yellow oil. 83% yield. IR ($CHCl_3$): 3584, 3347, 1592, 1351 cm^{-1}; ^1H NMR (acetone-d_6, δ): 7.67–7.64 (1H, m, aromatic proton); 7.40–7.23 (3H, m, aromatic protons); 3.56–3.50 (1H, d, J=17.9 Hz); 3.27–3.21 (1H, d, J=17.9 Hz); 2.94 (1H, bs, OH: exchange with D_2O); 1.94 (2H, q, J=7.4 Hz); 1.05 (3H, t, J=7.4 Hz). GC–MS (70 eV) *m/z* (rel. int.): 225 (M^+, 17), 208 (39), 207 (25), 196 (10), 190 (28), 180 (39), 178 (85), 171 (18), 169 (55), 153 (24), 152 (17), 151 (60), 150 (19), 139 (16), 138 (11), 137 (37), 134 (53), 111 (25), 75 (32), 57 (100), 43 (13). Anal. calcd for $C_{11}H_{12}NO_2Cl$: C, 58.67; H, 5.33; N, 6.22. Found: C, 58.61; H, 5.35; N, 6.20.

1.3.6. 3-(3-Nitrophenyl)-5-ethyl-5-hydroxy-2-isoxazoline (1f). Yellow oil. 70% yield. IR (CCl_4): 3595, 3464, 2971, 2928, 1534, 1464, 1349 924, 880 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 8.44–8.38 (1H, m, aromatic proton); 8.27–8.21 (1H, m, aromatic proton); 8.10–8.02 (1H, m, aromatic proton); 7.63–7.55 (1H, m, aromatic proton); 3.28 (2H, s); 3.10–2.80 (1H, bs, OH: exchange with D_2O); 2.04 (2H, q, J=7.5 Hz); 1.08 (3H, t, J=7.5 Hz). GC–MS (70 eV) *m/z* (rel. int.): 236 (M^+, 12), 219 (26), 207 (10), 189 (42), 180 (12), 162 (17), 76 (17), 57 (100). Anal. calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.95; H, 5.02; N, 11.90.

1.3.7. 3-(2,4,6-Trimethylphenyl)-5-ethyl-5-hydroxy-2-isoxazoline (1g). A 2.4 M solution of *n*-butyllithium in hexane (5.18 mL, 7.8 mmol) was added to diisopropylamine (1.1 mL, 7.8 mmol) in pentane (10 mL) at 0°C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and three dropping funnels. The mixture was stirred for 20 min and then the temperature was brought down to −78°C and the butanone (7.8 mmol) was added dropwise. The reaction mixture was stirred for 15 min before to add the 2,4,6-trimethylbenzonitrile oxide (2.6 mmol). The yellow reaction mixture kept at −78°C was stirred for 2 h. Then, the reaction was quenched by adding water. The reaction products were extracted three times with ethyl acetate. The organic phase was dried with anhydrous Na_2SO_4 and then evaporated. Column chromatography (silica gel, petroleum ether/ethyl acetate=7:3) of the residue affords the 3-aryl-5-hydroxy-5-alkyl-2-isoxazoline as white solid (82% yield). Mp 74–75°C; IR (CCl_4): 3598, 3446, 2970, 2882, 1614, 1463, 1332, 896 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 6.87 (2H, s, aromatic protons); 3.14–3.07 (1H, d, J=17.7 Hz); 3.00–2.95 (1H, d, J=17.7 Hz); 2.25 (1H, bs, OH: exchange with D_2O); 2.27 (3H, s); 2.24 (6H, s); 1.94 (2H, q, J=7.4 Hz); 1.07 (3H, t, J=7.4 Hz). GC–MS (70 eV) *m/z* (rel. int.): 233 (M^+, 33), 218 (22), 204 (13), 186 (34), 158 (100), 145 (27), 144 (30), 130 (25). Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15; N, 6.01. Found: C, 72.20; H, 8.11; N, 5.99.

The minor isomers **2** (see Table 1) were not isolated due to the rather small quantities that were formed, and so not fully characterized. Their formation was detected by GC–MS analysis. The two isomers **1** and **2** had quite distinct mass spectra (see above for the mass spectra of the isomer **1**).

1.3.8. 3-Phenyl-4,5-dimethyl-5-hydroxy-2-isoxazoline (2a). [GC–MS (70 eV) *m/z* (rel. int.)]: 191 (M^+, 4), 174 (36), 173 (32), 158 (20), 149 (67), 148 (48), 133 (18), 132 (32), 131 (43), 130 (100), 117 (17), 115 (19), 105 (14), 104 (34), 103 (69), 91 (14), 77 (60), 76 (19), 72 (21), 57 (13), 51 (23), 43 (64).

1.3.9. 3-Phenyl-4-ethyl-5-methyl-5-hydroxy-2-isoxazoline (2b). [GC–MS (70 eV) *m/z* (rel. int.)]: 205 (M^+, 45), 188 (32), 187 (24), 186 (10), 172 (14), 163 (38), 162 (11), 158 (10), 148 (84), 147 (27), 146 (19), 144 (45), 131 (15), 130 (100), 119 (16), 105 (19), 104 (45), 103 (44), 91 (12), 86 (18), 77 (43), 71 (28), 51 (20), 43 (44).

1.3.10. 3-Phenyl-4-(*n*-butyl)-5-methyl-5-hydroxy-2-isoxazoline (2c). [GC–MS (70 eV) *m/z* (rel. int.)]: 233 (M^+, 32), 216 (23), 215 (15), 177 (15), 175 (28), 174 (11), 172 (42), 160 (13), 159 (46), 148 (77), 144 (24), 131 (18), 130 (100), 117 (20), 115 (10), 104 (24), 103 (25), 91 (14), 77 (40), 71 (27), 43 (31).

1.3.11. 3-Phenyl-4-benzyl-5-methyl-5-hydroxy-2-isoxazoline (2d). [GC–MS (70 eV) *m/z* (rel. int.)]: 267 (M^+, 8), 250 (19), 249 (40), 248 (12), 224 (28), 208 (18), 207 (16), 206 (69), 146 (18), 145 (12), 131 (12), 105 (18), 104 (36), 103 (21), 91 (100), 77 (23), 43 (15).

1.3.12. 3-(2-Chlorophenyl)-4,5-dimethyl-5-hydroxy-2-isoxazoline (2e). [GC–MS (70 eV) *m/z* (rel. int.)]: 225 (M^+, 9), 209 (11), 208 (23), 207 (19), 192 (15), 190 (20), 185 (16), 183 (56), 182 (23), 174 (12), 167 (15), 166 (33), 165 (31), 164 (62), 148 (22), 140 (11), 139 (42), 138 (28), 137 (100), 115 (18), 111 (15), 102 (37), 76 (11), 75 (28), 72 (36), 57 (13), 51 (10), 43 (66).

1.3.13. 3-(3-Nitrophenyl)-4,5-dimethyl-5-hydroxy-2-isoxazoline (2f). [GC–MS (70 eV) *m/z* (rel. int.)]: 236 (M^+, 16), 219 (37), 218 (10), 194 (84), 193 (15), 178 (11), 177 (40), 176 (40), 175 (32), 148 (15), 145 (10), 130 (12), 129 (11), 118 (28), 115 (34), 103 (18), 102 (26), 91 (11), 77 (11), 76 (18), 75 (15), 72 (27), 57 (12), 50 (11), 43 (100).

1.3.14. 3-(2,4,6-Trimethylphenyl)-4,5-dimethyl-5-hydroxy-2-isoxazoline (2g). [GC–MS (70 eV) *m/z* (rel. int.)]: 233 (M^+, 60), 218 (27), 217 (11), 216 (51), 215 (15), 202 (11), 200 (12), 176 (25), 174 (17), 173 (28), 172 (100), 162 (16), 161 (13), 159 (19), 158 (70), 157 (18), 146 (25), 145 (76), 144 (28), 131 (13), 130 (58), 129 (12), 128 (15), 120 (12), 119 (12), 117 (12), 115 (20), 105 (14), 103 (13), 91 (24), 77 (16), 72 (12), 43 (30).

1.4. Synthesis of isoxazoles 3: general procedure

A solution of Na_2CO_3 (1.28 mmol) in water (10 mL) was added to a solution of 3-aryl-5-alkyl-5-hydroxy-2-isoxazoline (0.64 mmol) in methanol (10 mL). The reaction mixture was then heated under reflux for ca. 2 h. Then the methanol was evaporated under reduced pressure. The residue was treated with water and then the product was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure affording the isoxazoles in quantitative yield (Scheme 3).

1.4.1. 3-Phenyl-5-ethylisoxazole (3a). Yellow oil. IR (neat): 3040, 2978, 1602, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.80–7.76 (2H, m, aromatic protons); 7.46–7.39 (3H, m, aromatic protons); 6.27 (1H, s); 2.80 (2H, q, J=7.0 Hz); 1.33 (3H, t, J=7.0 Hz). GC–MS (70 eV) *m/z* (rel. int.): 173 (M^+, 59), 145 (18), 144 (100), 116 (28), 89 (11), 77 (31), 51 (11). Anal. calcd for $C_{11}H_{11}NO$: C, 76.30; H, 6.36; N, 8.09. Found: C, 76.21; H, 5.86; N, 8.01.

1.4.2. 3-Phenyl-5-(*n*-propyl)isoxazole (3b). Colourless oil. IR (neat): 3128, 3064, 2971, 2964, 2932, 2874, 1602, 1580, 1471, 1443, 1408, 950, 920, 799, 768, 693 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.84–7.73 (2H, m, aromatic protons); 7.45–7.37 (3H, m, aromatic protons); 6.27 (1H, s); 2.75 (2H, t, J=7.4 Hz); 1.73 (2H, sextet, J=7.4 Hz); 1.02 (3H, t, J=7.4 Hz). GC–MS (70 eV) *m/z* (rel. int.): 187 (M^+, 65), 159 (27), 158 (11), 145 (15), 144 (100), 117 (24), 116 (21), 89 (10), 77 (33), 51 (11). Anal. calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.49. Found: C, 76.96; H, 6.94; N, 7.42.

1.4.3. 3-Phenyl-5-(*n*-pentyl)isoxazole (3c). Colourless oil. IR (neat): 3053, 2950, 2928, 2860, 1602, 1580, 1471, 1443, 1408, 950, 915, 768, 693 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.83–7.74 (2H, m, aromatic protons); 7.47–7.35 (3H, m, aromatic protons); 6.25 (1H, s); 2.76 (2H, t, J=7.9 Hz); 1.83.1.62 (2H, m); 1.45–1.27 (4H, m); 0.86 (3H, t, J=6.9 Hz). GC–MS (70 eV) *m/z* (rel. int.): 215 (M^+, 66), 186 (12), 172 (22), 159 (54), 158 (12), 145 (15), 144 (98), 118 (13), 117 (100), 116 (18), 89 (12), 77 (42), 51 (11). Anal. calcd for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.11; H, 7.86; N, 6.38.

1.4.4. 3-Phenyl-5-(2-phenyl-1-ethyl)isoxazole (3d). White crystals. Mp 93–95°C; IR (KBr): 3115, 3063, 2940, 2923, 2896, 1600, 1577, 1496, 1470, 1455, 1444, 1407, 1261, 1083, 950, 916, 824, 768, 693 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.90–7.65 (2H, m, aromatic protons); 7.55–7.30 (3H, m, aromatic protons); 7.28–7.15 (5H, m, aromatic protons); 6.18 (1H, s); 3.12 (4H, m). GC–MS (70 eV) *m/z* (rel. int.): 249 (M^+, 91), 172 (10), 144 (14), 92 (14), 91 (100), 77 (23), 65 (11). Anal. calcd for $C_{17}H_{15}NO$: C, 81.93; H, 6.02; N, 5.62. Found: C, 81.70; H, 5.98; N, 5.55.

1.4.5. 3-(2-Chlorophenyl)-5-ethylisoxazole (3e). Colourless oil. IR (CCl_4): 3143, 3065, 2979, 2929, 2856, 1606, 1451, 1373, 1343, 949, 921, 877 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.73–7.64 (1H, m, aromatic protons); 7.48–7.40 (1H, m, aromatic protons); 7.38–7.26 (2H, m, aromatic protons); 6.41 (1H, s); 2.81 (2H, q, J=7.2 Hz); 1.35 (3H, t, J=7.2 Hz). GC–MS (70 eV) *m/z* (rel. int.): 207 (M^+, 34), 180 (37), 179 (12), 178 (100), 150 (23), 75 (9). Anal. calcd for $C_{11}H_{10}NOCl$: C, 63.77; H, 4.83; N, 6.76. Found: C, 63.75; H, 4.52; N, 6.48.

1.4.6. 3-(3-Nitrophenyl)-5-ethylisoxazole (3f). White crystals. Mp: 104–106°C; IR (CCl_4): 3061, 2927, 2890, 1604, 1468, 1375, 1349, 1099, 928, 875 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 8.63–8.56 (1H, m, aromatic protons); 8.33–8.23 (1H, m, aromatic protons); 8.20–8.12 (1H, m, aromatic protons); 7.66–7.57 (1H, m, aromatic protons); 6.38 (1H, s); 2.85 (2H, q, J=7.5 Hz); 1.35 (3H, t, J=7.5 Hz). GC–MS (70 eV) m/z (rel. int.): 218 (M^+, 32), 189 (100), 188 (13), 159 (14), 143 (27), 76 (12), 57 (12). Anal. calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.59; N, 12.84. Found: C, 60.51; H, 4.56; N, 12.80.

1.4.7. 3-(2,4,6-Trimethylphenyl)-5-ethylisoxazole (3g). Yellow oil. IR (CCl_4): 3043, 2978, 2924, 2858, 1615, 1456, 1394, 1379, 1337, 934, 889 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 6.91 (2H, s, aromatic protons); 5.89 (1H, s); 2.83 (2H, q, J=7.5 Hz); 2.30 (3H, s); 2.13 (6H, s); 1.34 (3H, t, J=7.5 Hz). GC–MS (70 eV) m/z (rel. int.): 215 (M^+, 66), 187 (17), 186 (100), 159 (25), 158 (71), 144 (22), 143 (19), 115 (16), 91 (16). Anal. calcd for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.25; H, 7.58; N, 6.12

1.5. Reaction of 3-phenyl-5-ethylisoxazole with RX (CH_3I or $PhCH_2Br$) in the presence of LDA or LTMP in THF

A 2.21 M solution of *n*-butyllithium in hexane (0.196 mL, 0.4335 mmol) was added to diisopropylamine (0.061 mL, 0.4335 mmol) in THF (2 mL) at 0°C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and three dropping funnels. After 15 min the temperature was brought down to −78°C and the 3-phenyl-5-ethylisoxazole (50 mg, 0.289 mmol) in THF (2 mL) was added dropwise. The red reaction mixture kept at −78°C was stirred for 2 h before to add CH_3I or $PhCH_2Br$ (2.89 mmol). The reaction mixture was allowed to reach room temperature and then quenched by adding aq. NH_4Cl. The two phases were separated and aqueous phase was extracted three times with ethyl acetate. The organic extracts combined were dried with anhydrous Na_2SO_4 and then evaporated. Column chromatography (silica gel, petroleum ether/ethyl acetate=7:3) of the residue affords the 3-phenyl-5-(2-propyl)-isoxazole or 3-phenyl-5-(1-phenyl-2-propyl)isoxazole in 78% to quantitative yield (Table 2).

1-Bromo-1,2-diphenylethene (up to 12%) is also formed when the benzyl bromide is used as electrophile (footnote c, Table 2), whose formation can be ascribed to some competitive metallation of benzyl bromide by LDA followed by reaction with benzyl bromide itself.

1.5.1. 3-Phenyl-5-(2-propyl)-isoxazole (4a). 78% (LDA) and 97% (LTMP) yield. Colourless oil. IR (neat): 3127, 3064, 2971, 1599, 1578, 1475, 1441, 1408, 916, 802, 768, 694 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.86–7.68 (2H, m, aromatic protons); 7.52–7.30 (3H, m, aromatic protons); 6.26 (1H, s); 3.02 (1H, heptet, J=6.9 Hz); 1.29 (6H, d, J=6.9 Hz). GC–MS (70 eV) m/z (rel. int.): 187 (M^+, 41), 144 (100), 116 (16), 89 (6), 77 (20). Anal. calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.49. Found: C, 76.95; H, 6.91; N, 7.60.

1.5.2. 3-Phenyl-5-(1-phenyl-2-propyl)isoxazole (4b). White crystals. 81% yield. Mp 76–77°C; IR (KBr): 3125, 3061, 2965, 2920, 1596, 1577, 1453, 1401, 1262, 1087, 1024, 800, 767, 695 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 7.81–7.76 (2H, m, aromatic protons); 7.75–7.40 (3H, m, aromatic protons); 7.37–7.10 (5H, m, aromatic protons); 6.22 (1H, d, J=0.6 Hz); 3.40–3.10 (2H, m; 1H of C*H*CH_3 and 1H of CH_2Ph); 2.95–2.80 (1H, dd, J=8.1 and 13.3 Hz, CH_2); 1.31 (3H, d, J=6.8 Hz). GC–MS (70 eV) m/z (rel. int.): 263 (M^+, 80), 172 (10), 91 (100), 77 (14). Anal. calcd for $C_{18}H_{17}NO$: C, 82.13; H, 6.46; N, 5.32. Found: C, 82.20; H, 6.53; N, 5.11.

1.6. Reaction of 3-phenyl-5-ethylisoxazole with CH_3I in the presence of *n*-butyllithium (or *t*-butyllithium) in THF

A 2.18 M solution of *n*-butyllithium in hexane (0.159 mL, 0.347 mmol) was added to a solution of 3-phenyl-5-ethyl-isoxazole (50 mg, 0.289 mmol) in THF (2 mL) at −78°C under nitrogen, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and three dropping funnels. The red reaction mixture was kept at 78°C for 1 h (3 h in the case of *t*-butyllithium). Then, CH_3I (0.18 mL, 2.89 mmol) was added. The reaction mixture was allowed to reach room temperature and then quenched by adding aq. NH_4Cl. The two phases were separated and aqueous phase was extracted three times with ethyl acetate. The organic extracts combined were dried with anhydrous Na_2SO_4 and then evaporated. Column chromatography (silica gel, petroleum ether/ethyl acetate=9:1) of the residue affords a mixture of 3-phenyl-5-(2-propyl)-isoxazole and 3-phenyl-4-methyl-5-ethylisoxazole in 40 and 14% yield (or 32 and 8% in the case of *t*-butyllithium), respectively.

1.6.1. 3-Phenyl-4-methyl-5-ethylisoxazole (5). 8 or 14% yield (Table 2). Colourless oil. ^1H NMR ($CDCl_3$, δ): 7.68–7.61 (2H, m, aromatic protons); 7.50–7.43 (3H, m, aromatic protons); 2.81–2.70 (2H, q, J=7.59 Hz, CH_2); 2.06 (3H, s, CH_3); 1.34–1.26 (3H, t, J=7.59 Hz, CH_2CH_3). GC–MS (70 eV) m/z (rel. int.): 187 (M^+, 45), 159 (12), 158 (100), 144 (35), 131 (18), 130 (36), 104 (13), 77 (52), 51 (19).

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