AN UNEXPECTED TRANSFORMATION DURING THE SYNTHESIS OF 3,5-DISUBSTITUTED ISOXAZOLES

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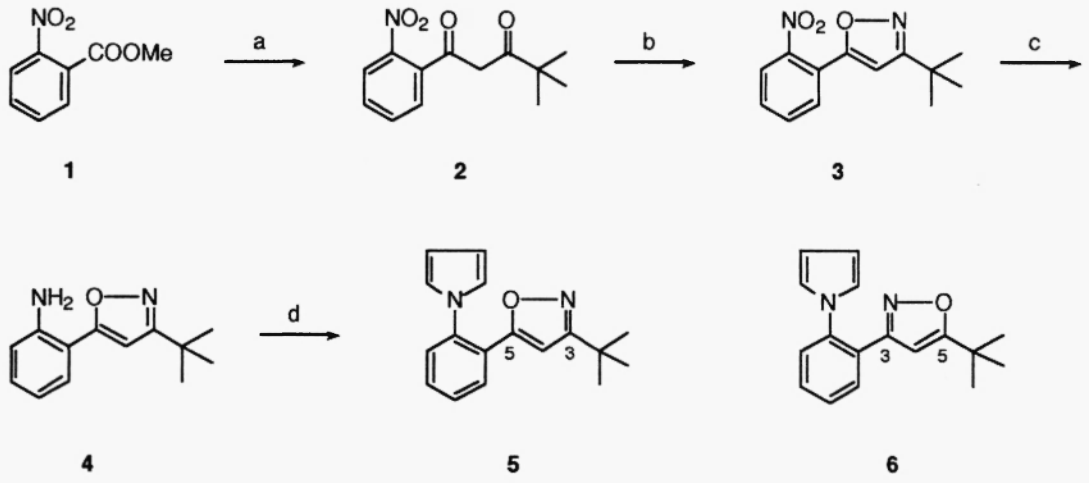
Abstract: An attempt to synthesize 3-(*tert*-butyl)-5-phenylisoxazole derivative **5** from 4,4-dimethyl-1-(2-nitrophenyl)pentane-1,3-dione **2** or from 3-*tert*-butyl-5-(2-pyrrol-1-yl-phenyl)-4,5-dihydroisoxazole-5-ol **9** produced only 5-*tert*-butyl-3-(2-pyrrol-1-yl)isoxazole **6**. The structure was confirmed by HMBC NMR data and comparison with model compounds 5-*tert*-butyl-3-phenylisoxazole and 3-*tert*-butyl-5-phenylisoxazole.

During the course of a recent project, we needed the 3-(*tert*-butyl)-5-phenylisoxazole **5** as a target molecule. Our synthetic approach to **5** was based on a classical strategy for the construction of the isoxazole heterocycle, condensation of β-diketone **2** with hydroxylamine (1). The literature reveals that reaction of 1-alkyl-3-aryl β-diketones with hydroxylamine produces 3-alkyl-5-arylisoxazoles (2-5), however, in certain instances when the alkyl group is *tert*-butyl, mixtures of 3-alkyl-5-aryl and 3-aryl-5-alkylisoxazoles are obtained (6).

In our initial approach to the construction of **5** we planned to assemble the isoxazole ring first and then introduce the pyrrole ring at the last step in the synthesis (Scheme 1). The isoxazole precursor, diketone **2**, is prepared in 47% yield by reaction of methyl 2-nitrobenzoate **1** with two equivalents of pinacolone enolate. Condensation of **2** with hydroxylamine hydrochloride in refluxing ethanol produces one isoxazole product. Reduction of the nitro group to the amine followed by treatment with 2,5-dimethoxytetrahydrofuran furnishes the pyrrole.

Detailed HMBC NMR evaluation clearly showed that the product had the *tert*-butyl group on the carbon that resonated at lowest field. Published carbon NMR data (7) indicate that in almost every instance the chemical shift for the oxygenated carbon, C-5, is at lower field than the shift for C-3 suggesting the structure was the 3-aryl-5-alkyl isomer **6** and not the desired product **5**.

Scheme 1



(a) pinacolone, LDA, –78° → rt, 18h; (b) NH_2OH•HCl, ethanol, reflux, 24 h; (c) H_2 (1 atm), PtO_2, ethanol, 90 min; (d) 2,5-dimethoxy-tetrahydrofuran, HOAc, 90–95°C, 2h.

In order to circumvent the unwanted regiochemical outcome of the addition of hydroxylamine to **2**, we chose a more convergent, unequivocal approach to **5** (Scheme 2). In this route the carbon-nitrogen bond of the oxime is fixed adjacent to the *tert*-butyl group in one of the reactants, pinacolone oxime (**8b**). Consequently, when ester **7** is allowed to react with the dianion of **8**, the 5-hydroxy-2-isoxazoline **9** is produced in 75% yield. This is not surprising since it has been reported that when β-keto oximes contain one or more bulky groups, the ring tautomer is favored over the chain tautomer. In fact, if there is a *tert*-butyl group present, the ring tautomer is formed exclusively (8).

The structure of **9** was confirmed from HMBC NMR correlation data. A cross peak is observed between an aromatic proton and the acetal carbon at δ = 103.0. This correlation could arise only from structure **9**. Dehydration of **9** under acidic conditions (9) produces a single product in 78% yield. Analysis of the physical and spectral data surprisingly showed them to be identical to the data for **6** obtained from the route outlined in Scheme 1. It is possible that **9**, rather than dehydrating to give **5**, hydrolyzes to a β-diketone and the free hydroxylamine readily adds to the phenyl ketone then dehydrates to form **6**.

Scheme 2

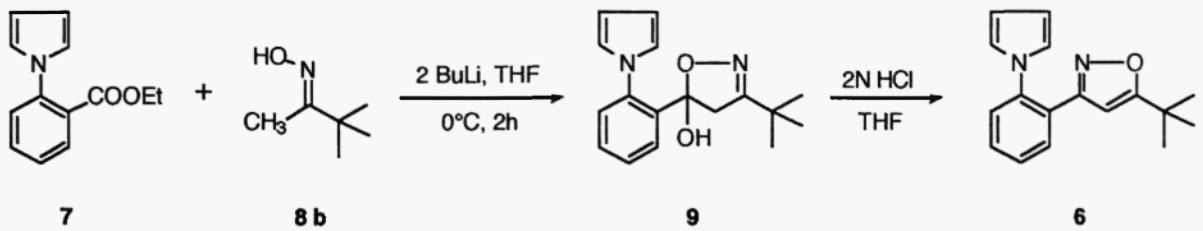
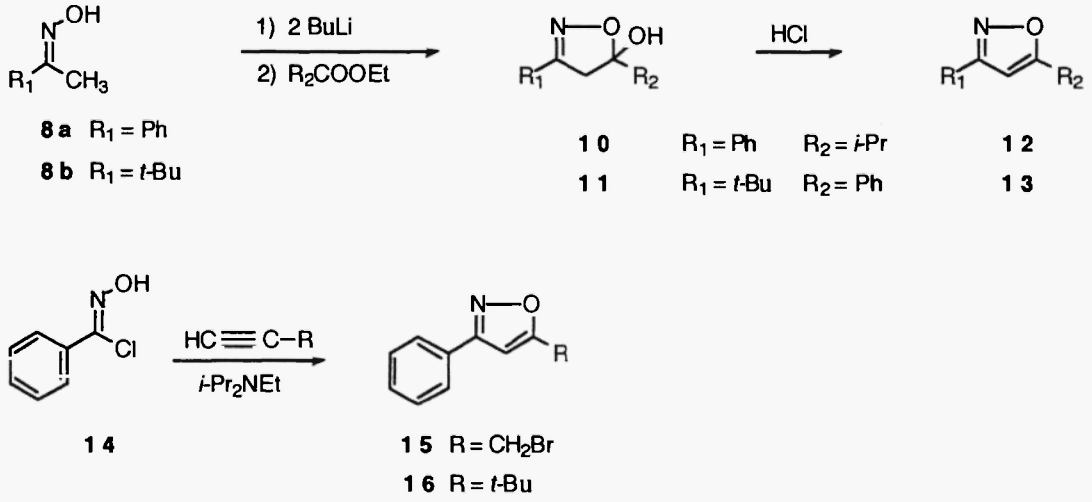


Table 1. Carbon-13 Shifts of C-3 and C-5 Carbon Atoms of Isoxazoles

No	C-3 (ppm)	C-5 (ppm)
6	164.1	173.7
9	168.2	105.3
10	157.1	111.3
11	167.1	106.8
12	162.2	179.3
13	172.7	169.3
15	163.7	170.1
16	162.5	182.2

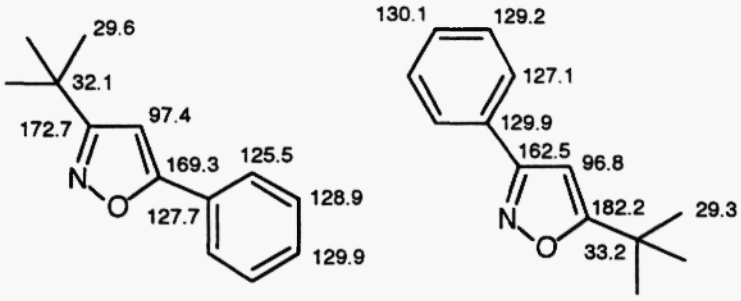
In order to insure that this anomalous result was not coincidental equivalence in the spectra, we synthesized a series of simple 3-phenyl-5-alkyl and 5-phenyl-3-alkylisoxazoles by either oxime dianion chemistry (10) or nitrile oxide cycloaddition to acetylenes (11) (Scheme 3).

Scheme 3



The observed carbon-13 NMR data for two possible *tert*-butyl isoxazoles **13** and **16** are shown in Figure 1. HMBC NMR data were evaluated and compared with compound **6**. While compound **13** shows one of the rare instances where the oxygenated carbon is to higher field than the imine carbon, it yields data consistent with expected additivity correlations based upon phenyl derivatives (12). Compound **16** gives rise to carbon-13 shifts consistent with other alkyl substituted isoxazoles indicating that the *tert*-butyl group introduces no anamolous effects.

Figure 1. Carbon-13 Assignments for Isomeric Isoxazoles 13 and 16



13 **16**

Experimental

Proton NMR and HMBC data were measured using a DMX500 spectrometer operating at 500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C with a triple inverse gradient probe (^{1}H, ^{13}C, ^{15}N). The temperature of the samples was regulated at 300K using $CDCl_3$ as the solvent. The 90° ^{1}H pulse for the probe was 10.3 msec at a power level of 6 dB and the 90° ^{13}C pulse was 10 msec at a power level of 0 dB. Proton spectra were recorded with a spectral width of 7507 Hz and a 45° observation pulse. The HMBC experiments were acquired using a pulse field gradients to eliminate spectral artefacts. The spectral widths were set for 6009 Hz in the proton dimension and 26411 Hz in the carbon dimension. The $^{1}J_{CH}$ filter (D2) was set for 3.57 msec (135 Hz) and the delay for the evolution of long range couplings (D6) was set for 50 msec (10 Hz). A 3 sine gradient pulse program was employed for a duration of 1 msec each and amplitudes of 50%, 30% and 40%. The data matrix was 2048 data points by 256 increments, 4 scans per increment. The data were processed using a sine squared function that was shifted by 90°. Proton and carbon NMR spectra were also measured using an AC300 spectrometer operating at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C with a 5mm QNP probe (^{1}H, ^{13}C, ^{31}P and ^{19}F). The 90° ^{1}H pulse for the probe was 10.5 msec and the 90° ^{13}C pulse was 6 msec.

4,4-Dimethyl-1-(2-nitrophenyl)pentane-1,3-dione (2). To a solution of diisopropylamine (8.0 g, 0.04 mol) in THF (90 ml) at 0°C under a blanket of argon was added *n*-butyllithium (5.1 g, 0.08 mol, 1.6M in hexane). The solution was cooled to -78°C then a solution of pinacolone (8.0 g, 0.08 mol) in THF (35 ml) was added dropwise. After stirring at -78°C for 30 min, a solution of methyl 2-nitrobenzoate (7.3 g, 0.04 mol) in THF (30 ml) was added dropwise. The cooling bath was removed and the reaction was stirred at rt for 24 h. Saturated NH_4Cl was added and the mixture was extracted with MTBE (200 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford crude diketone **2** as a dark oil. Column chromatography (10% EtOAc/hexane) provided **2** as an oil (4.7 g, 47%); ^{1}H NMR ($CDCl_3$) δ 15.55 (s, 1 H), 7.93 (d, 1 H), 7.71-7.57 (m, 3 H), 5.91 (s, 1 H), 1.23 (s, 9 H).

Reaction of 2 With Hydroxylamine. A mixture of **2** (4.5 g, 0.018 mol) and $NH_2OH{\cdot}HCl$ (1.25 g, 0.018 mol) in ethanol (100 ml) was refluxed for 24 h. The solvent was removed under reduced pressure to afford nearly pure isoxazole (4.2 g, 95%) as an oil. An analytical sample was chromatographed on a Rainin HPXL apparatus (10% EtOAc/hexane); ^{1}H NMR ($CDCl_3$) δ 7.84-7.52 (m, 4 H), 6.36 (s, 1 H), 1.37 (s, 9 H).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.31; H, 5.77; N, 11.00.

Reduction of Nitro Group of Putative 3. A mixture of the nitro isoxazole (1.8 g, 7.3 mmol) and platinum oxide (180 mg) in ethanol (40 ml) was stirred under a hydrogen atmosphere for 20 min. The catalyst was filtered and the solvent was removed under reduced pressure to give the amine (1.4 g, 87%) as an oil; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1 H), 7.19 (m, 1 H), 6.76 (m, 2 H), 6.36 (s, 1 H), 4.59 (s, broad, 2 H), 1.38 (s, 9 H). MS (Cl) m/z 217 (MH^+) (100), 161 (14.6), 120 (19.8). This material was used in the next step without further purification.

5-*tert*-Butyl-3-(2-pyrrol-1-yl)isoxazole (6). A mixture of the above amine (2.3 g, 10.6 mmol) and 2,5-dimethoxytetrahydrofuran (1.7 g, 12.9 mmol) in acetic acid (4 ml) was stirred at 90-95°C for 2 h. The acetic acid was removed from the dark-colored solution under reduced pressure. The residual oil was dissolved in MTBE (50 ml) and the solution was washed with saturated $NaHCO_3$ (30 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give essentially pure product. Polar material was removed by filtering through a plug of silica gel (CH_2Cl_2) to afford **6** as a solid (1.8 g, 64%); mp 84-86°C; ^{1}H NMR ($CDCl_3$) δ 8.1 (m, 1 H), 7.4 -7.6 (m, 3 H), 6.64 (m, 2 H), 6.32 (m, 2 H), 4.92 (s, 1 H),1.22 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 173.7, 164.1, 138.7, 130.4, 128.8, 128.4, 128.1, 125.9, 121.6, 109.7, 100.5, 32.3, 29.5.
Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10,52. Found: C, 76.63; H, 6.81; N, 10.32.

3-*tert*-Butyl-5-(2-pyrrol-1yl-phenyl)-4,5-dihydroisoxazole-5-ol (9). To a solution of pinacolone oxime (1.5 g, 13 mmol) in THF (30 ml) at 0°C was added dropwise *n*-butyllithium (1.7 g, 26 mmol, 1.6M in hexane). After stirring at 0°C for 2 h, a solution of **7** (13) (1.4 g, 6.5 mmol) in THF (5 ml) was added dropwise. Stirring was continue at 0°C for an additional 2 h. Saturated NH_4Cl was added and the mixture was extracted with MTBE (100 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford 2.4 g of crude product. The oil was chromatographed on a Rainin HPXL apparatus (15% EtOAc/hexane) to afford **9** as a solid (1.36 g, 75%); mp 110-112°C; ^{1}H NMR ($CDCl_3$) δ 7.2 -7.65 (m, 8 H), 3.03 -3.35 (m, 2 H), 1.23 (s, 9 H). MS (Cl) m/z 284 (MH^+) (5), 267 (100).
Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.09; N, 9.85. Found: C, 71.75; H, 7.30; N, 9.71.

5-*tert*-Butyl-3-(2-pyrrol-1-yl)isoxazole (6). To a solution of **9** (3.5 g, 12.4 mmol) in THF (50 ml) was added 2N HCl (1.0 ml) and the mixture was stirred at rt for 2 h. Saturated sodium chloride (50 ml) was added and the mixture was extracted into MTBE (100 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give essentially pure product. Polar material was removed by filtering through a plug of silica gel (CH_2Cl_2) to afford **6** as a solid (2.55g, 78%); mp 84-87°C; MS (Cl) m/z 267 (MH^+) (100). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.70; H, 6.92; N, 10.20.

5-Isopropyl-3-phenyl-4,5-dihydroisoxazol-5-ol (10). To a solution of acetophenone oxime (2.0 g, 14.8 mmol) in THF (80 ml) at 0°C was added dropwise *n*-butyllithium (2.18 g, 34 mmol, 1.6M in hexane). The yellow solution was allowed to warm to rt and stirred there for 1 h then the reaction mixture was cooled to -78°C. Ethyl isobutyrate (1.9 g, 16.3 mmol) was added and the solution was stirred at -78°C for 30 min and at

0°C for 30 min. Saturated NH_4Cl was added and the mixture was extracted with MTBE (80 ml). The organic phase was dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford the crude product. The oil was purified by flash chromatography (10% EtOAc/hexane) to afford **10** as a solid (1.7 g, 56%); mp 96-98°C; IR (KBr) 3268 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.68 (m, 2 H), 7.39 (m, 3 H), 3,22 (q, 2 H), 2.81 (s, 1 H), 2.19 (m, 1 H), 1.12 (d, 3 H), 1.03 (d, 3 H). MS (DCI) m/z 206 (MH^+) (73). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.42; H, 7.26; N, 6.86.

3-*tert*-Butyl-5-phenyl-4,5-dihydroisoxazol-5-ol (11). The reaction was performed similar to the preparation of **9** using pinacolone oxime (2.3 g, 20 mmol), methyl benzoate (1.36 g, 10 mmol), and *n*-butyllithium (2.56 g, 40 mmol) to give **11** as a waxy solid (1.63 g, 74%); mp 69-72°C; ^1H NMR ($CDCl_3$) δ 7.98 (m, 2 H), 7.2 -7.42 (m, 4 H), 2.6-2.8 (m, 2 H), 1.09 (s, 9 H). MS (DCI) m/z 220 (MH^+) (100), 202 (45), 146 (10). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.07; H, 7.64; N, 6.41. Found: C, 71.20; H, 7.81; N, 6.39.

5-Isopropyl-3-phenylisoxazole (12). To a solution of **10** (1.7 g, 8.3 mmol) in THF (40 ml) was added 2N HCl (5 ml) and the mixture was stirred at rt for 18 h. The solvent was removed under reduced pressure and the residue was filtered through a plug of silica gel (CH_2Cl_2) to give **12** as a pale yellow oil (1.13 g, 73%); ^1H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.47 (m, 3 H), 6.30 (s, 1 H), 3.14 (m, 1 H), 1.40 (d, 6 H). MS (DCI) m/z 188 (MH^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.98; H, 7.03; N, 7.49.

3-*tert*-Butyl-5-phenylisoxazole (13). The reaction was performed similarly as that of **12** with a reaction time of 2 h to give **13** in 89% yield; mp 73-76°C; ^1H NMR ($CDCl_3$) δ 7.4 (m, 3 H), 7.8 (m, 2 H), 6.45 (s, 1 H), 1.4 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.7, 169.3, 130.1, 129.2, 125.8, 97.5, 32.3, 29.6. MS (DCI) m/z 202 (MH^+) (3), 116 (100).

5-Bromomethyl-3-phenylisoxazole (15). To a solution of **14** (14) (10.0 g, 64.3 mmol) and propargyl bromide (10.7 g, 90 mmol) in anhydrous ether (150 ml) at -5°C was added dropwise a solution of diisopropylethylamine (11.63 g, 90 mmol) in ether (25 ml) over a period of 30 min. The reaction mixture was stirred at 0°C for 15 min then at rt for 2 h. Water was added and the mixture was extracted into MTBE (150 ml). The organic phase was washed with saturated NaCl (150 ml) and was dried ($MgSO_4$). The solvent was removed under reduced pressure and the residual oil was flash chromatographed (10% EtOAc/hexane) to give **15** as a white solid (10.52 g, 69%); mp 86-87°C; ^1H NMR ($CDCl_3$) δ 7.83 (m, 2 H), 7.50 (m, 3 H), 6.68 (s, 1 H), 4.53 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 163.7, 130.0, 129.3, 127.0, 102.3, 18.9. MS (DCI) m/z 240 (82), 238 (MH^+) (100), 194 (31), 160 (18). Anal. Calcd for $C_{10}H_8NOBr$: C, 50.45; H, 3.39; N, 5.88; Br, 33.56. Found: C, 50.18; H, 3.30; N, 5.78; Br, 33.56.

5-*tert*-Butyl-3-phenylisoxazole (16). To a solution of **14** (14) (2.37 g, 15.2 mmol) and *tert*-butyl acetylene (1.0 g, 12.2 mmol) in anhydrous ether (15 ml) at -5°C was added dropwise a solution of diisopropylethylamine (2.04 g, 15.8 mmol) in ether (5 ml) over a period of 20 min. The reaction mixture was stirred at 0°C for 15 min then at rt for 24 h. Water was added and the mixture was extracted into MTBE (30 ml). The organic phase was washed with saturated NaCl (25 ml) and was dried ($MgSO_4$). The solvent was removed

under reduced pressure and the residual oil was flash chromatographed to give **16** as a white solid (700 mg, 29%); mp 59-61°C; ^{1}H NMR ($CDCl_3$) δ 7.8 (m, 2 H), 7.5 (m, 3 H), 6.3 (s, 1 H), 1.41 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 182.2, 162.5, 130.1, 129.9, 129.2, 127.0, 96.5, 33.1, 29.1. MS (DCI) m/z 201 (MH^+) (100). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.52; H, 7.53; N, 6.98.

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