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4-Bromo-2,3-dihydroisoxazoles: synthesis and application in halogen-lithium exchange reactions

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ABSTRACT

The synthesis of novel types of 4-bromo-2,3-dihydroisoxazoles using pyridinium tribromide in the presence of base is described. Reactivity of the initial substrates and the yields depend on the substituent at C3. To demonstrate a practical scope of the 4-bromo-substituted 2,3-dihydroisoxazoles, representative 2-benzyl-4-bromo-3,5-diphenyl-2,3-dihydroisoxazole is subjected to halogen-lithium exchange reaction. The corresponding (2,3-dihydroisoxazol-4-yl)lithium reacts with three selected electrophiles to afford 4-substituted 2,3-dihydroisoxazoles in moderate yields.

1. Introduction

Small metalated heterocycles represent attractive substrates in organic synthesis due to their wide applicability in forming new carbon–carbon bonds.[1] Specifically, five-membered aromatic (isoxazol-4-yl)lithium species **1** (Fig. 1) are powerful building blocks in medicinal chemistry and play an important role as promising substrates in the processes of screening for potent pharmacological candidates.[2] For instance, Valdecoxib (nonsteroidal antiinflammatory drug) and Oxacillin (β-lactamase-resistant antibiotic) have been recently synthesized from 4-bromo-5-methylisoxazole **2** using bromine-lithium exchange reaction at the 4-position also.[2a] On the other hand, a method for the successful preparation of nonaromatic lithiated isoxazolines **3** has not been described to date.

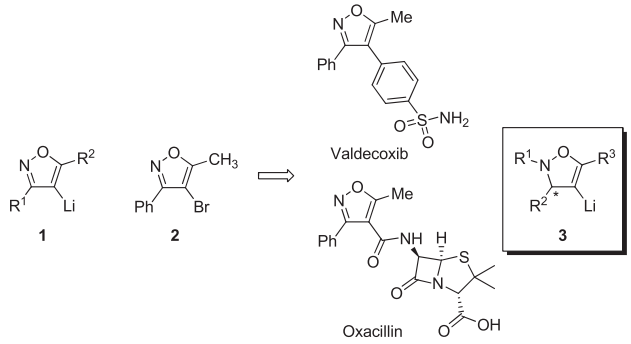
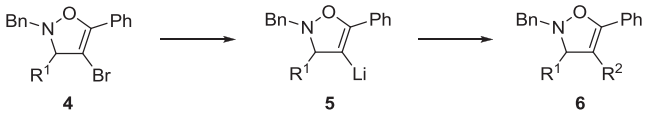


Fig. 1. (Isoxazol-4-yl)lithium species as suitable substrates for biologically active molecules.

Based on our interest in the field of 2,3-dihydroisoxazoles,[3] we investigated the synthesis of such novel lithiated heterocycles. In this paper, we report on the preparation of *N*-benzyl-4-bromo-2,3-dihydroisoxazoles **4** by means of bromination reactions of 4-unsubstituted 2,3-dihydroisoxazoles, and on their utilization in bromine-lithium exchange reactions to afford (2,3-dihydroisoxazol-4-yl)lithium compounds **5** as suitable substrates for carbon–carbon bond formation at C4 (Scheme 1). The presented synthetic route provides the possibility for 4-substituted 2,3-dihydroisoxazoles **6** that could be hard to prepare by other methods.



Scheme 1. General synthetic route to 4-substituted 2,3-dihydroisoxazoles via bromine-lithium exchange.

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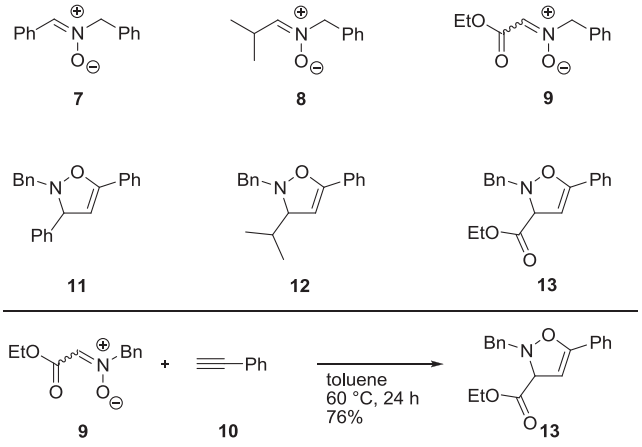
0040-4020/

2. Results and discussion

2.1. Synthesis of 2,3-dihydroisoxazoles

In accordance with the literature, the starting *N*-benzyl-2,3-dihydroizoxazoles **11** and **12** were readily available from the corresponding nitrones (Scheme 2).[4] The reactions of nitrones **7**[4b] and **8**[5] with phenylacetylene (**10**) in the presence of $Zn(OTf)_2$ afforded propargylic *N*-hydroxylamines,[4b] which upon zinc iodide catalyzed cyclization gave 2,3-dihydroizoxazoles **11** and **12** in very good yields (89% and 92%) nearly consistent with published results.[4c] 2,3-Dihydroizoxazole **13** was prepared via direct 1,3-dipolar cycloaddition of nitrone **9**[6] with phenylacetylene (**10**) in satisfactory 76% yield (Scheme 2). Contrary to previously published procedures for **13**,[7] the presented reaction was performed in toluene at 60 °C in 24 h without catalyst.

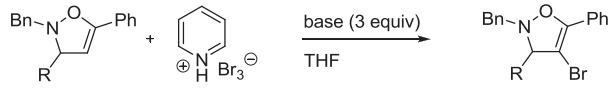


Scheme 2. Starting *N*-benzyl-2,3-dihydroisoxazoles prepared from the corresponding nitrones.

2.2. Bromination reactions

Only a few reports on the synthesis of 4-halogen-substituted 2,3-dihydroizoxazoles have appeared to date. In general, such compounds were considered to be unstable and therefore not applicable in subsequent reactions. They were obtained by reductions of the corresponding isoxazolium salts with $LiAlH_4$ and $NaBH_4$,[8a] or by their reactions with organometallic reagents,[8b] and through the iodocyclization of the propargylic *N*-hydroxylamines in the presence of ICl.[8c] As mentioned earlier, our experiences with the chemistry of 2,3-dihydroisoxazoles inspired us to examine a chemical behavior of such compounds in bromination reactions, with the goal to prepare 4-bromo-2,3-dihydroisoxazoles as suitable starting substrates for halogen-lithium exchange reactions.

At the beginning, we focused our attention on searching for a suitable bromination agent. First attempts were carried out with model dihydroisoxazole **11** (0.16 mmol scale) in anhydrous THF in the presence of triethylamine at 0 °C. NBS did not work, and the use of bromine led to a rapid decomposition of **11** without any evidence of the desired product. Fortunately, pyridinium tribromide (**14**) reacted satisfactorily to afford 4-bromo-2,3-dihydroisoxazole **15** (Scheme 3). A dropwise addition of freshly prepared THF solution of **14** was preferred, compared to a solid. Solvents such as NMP, CH_3CN, $CHCl_3$ and CH_2Cl_2 were also tested, however they were found to be unsuitable. The best results in terms of chemical yield and purity were obtained, when the reaction was performed at −40 °C and with 3 equiv of triethylamine. It is worth noting that the elimination also proceeded without any additional base, however the desired product **15** gradually decomposed. Most likely, released hydrobromic acid caused the quarternisation of N2, which resulted in ring-opening reactions. The use of DBU or pyridine did not have a positive effect on the reaction course. Finally, we prepared dihydroisoxazole **15** in satisfactory 60% yield. The reaction performed in less concentrated solution led to higher yield of **15** (60% at 0.05 M, 26% at 0.1 M and 25% at 0.5 M). With optimized reaction conditions in hand, we scaled up the reaction of **11** (1.6 mmol). Surprisingly, the yield dropped dramatically to 13%. Based on our positive experiences with 2-chloropyridine in elimination reactions,[3d] we have replaced triethylamine for this base. Thus, the bromination of **11** with 1.1 equiv of pyridinium tribromide (**14**) and 3 equiv of 2-chloropyridine in anhydrous THF at −40 °C gave 4-bromo-2,3-dihydroisoxazole **15** in 53% yield (Scheme 3). Contrary to bromination of **11**, the reactions of 2,3-dihydroisoxazoles **12** and **13**, bearing isopropyl and ethoxycarbonyl groups at C3, proceeded slower at −40 °C, and therefore needed to be performed at higher temperature, and moreover with a larger amount of pyridinium tribromide (**14**). Interestingly, triethylamine was again a superior base to 2-chloropyridine. Finally, desired 4-bromo-2,3-dihydroisoxazoles **16** and **17** were prepared in 66% and 50% yields, respectively (Scheme 3). The bromination at C4 was confirmed by ^1H and ^{13}C NMR experiments as follows. Signal of the H-4 proton disappeared and the multiplicity of the H-3 proton of **15** was simplified (singlet, δ=4.98 ppm) compared to H-3 and H-4 protons of starting 2,3-dihydroisoxazole **11**. Furthermore, the signals of C-4 and C-5 were shifted to low field (C-4, **11**: δ=95.9 ppm; **15**: δ=88.4 ppm and C-5, **11**: δ=153.0 ppm; **15**: δ=147.8 ppm). The presence of the bromo atom was clearly confirmed by HRMS.

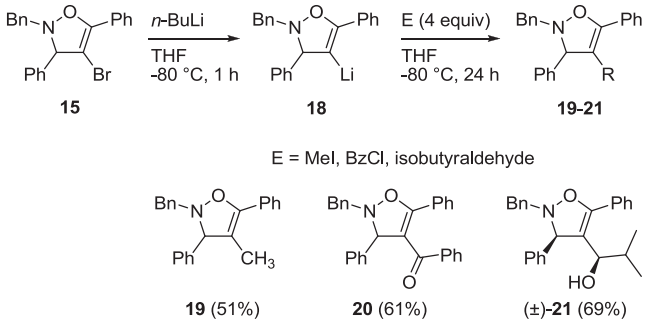


		T [°C]	r. time	base		
11 R = Ph	1.1 equiv	-40	24 h	2-ClPy	**15** R = Ph	53%
12 R = *i*-Pr	2.0 equiv	rt	5 h	Et_3N	**16** R = *i*-Pr	66%
13 R = CO_2Et	2.5 equiv	rt	4 h	Et_3N	**17** R = CO_2Et	50%

Scheme 3. Bromination reactions of 2,3-dihydroisoxazoles into the 4-position.

2.3. Bromine-lithium exchange reactions

To further demonstrate a practical scope of the 4-bromo-substituted 2,3-dihydroisoxazoles, we focused our attention on bromine-lithium exchange reactions. As shown in Scheme 4, representative 2,3-dihydroisoxazole **15** was treated with *n*-BuLi in anhydrous THF at −80 °C. The rate of lithium insertion was monitored by TLC (hexanes/CH_2Cl_2, 70:30) and HPLC-MS. The quenching of an analytical sample with satd aq NH_4Cl solution caused a rapid hydrolysis of lithium species **18**, affording 4-unsubstituted 2,3-dihydroisoxazole **11**. A starting substrate was completely consumed after stirring for one hour. Subsequently, a neat electrophile was added dropwise and the stirring continued for 24 h at −80 °C. Iodomethane, benzoyl chloride and isobutyraldehyde were selected as appropriate electrophiles due to their good reactivity. Three representative 2,3-dihydroisoxazoles **19**, **20** and **21** were successfully prepared in moderate 51%, 61% and 69% yields, respectively (Scheme 4). Moreover, the reaction with isobutyraldehyde exclusively provided single isomer. Despite the complete bromine-lithium exchange, 2,3-dihydroisoxazole **11** was detected in all cases, even though 4 equiv of each electrophile were used and the reaction time was 24 h.[9]



Scheme 4. Reagents and conditions: a) *n*-BuLi (2.5 M in hexane), THF, −80 °C; b) electrophile (E), THF, −80 °C.

3. Conclusions

In conclusion, novel bromination of 2,3-dihydroisoxazoles into the 4-position using pyridinium tribromide in the presence of base is presented. Three representative 4-bromo-2,3-dihydroisoxazoles are prepared and isolated in moderate yields for the first time. Reactivity of the initial substrates and the yields depend on the substituent at C3. To demonstrate a practical scope of the 4-bromo-substituted 2,3-dihydroisoxazoles, representative 2-benzyl-4-bromo-3,5-diphenyl-2,3-dihydroisoxazole is subjected to halogen-lithium exchange reaction. The corresponding (2,3-dihydroisoxazol-4-yl)lithium reacts with three selected electrophiles to afford 4-substituted 2,3-dihydroisoxazoles in moderate yields. The presented synthetic route offers an alternative method for the preparation of 2,3-dihydroisoxazoles that can be difficult to obtain with 1,3-dipolar cycloadditions of nitrones with 1,2-disubstituted alkynes.

4. Experimental section

4.1. General

All melting points were measured on a Melting Point B-540 apparatus (Büchi) and are uncorrected. HRMS analyses were performed on Orbittrap Velos Pro spectrometer (Thermo Fisher Scientific). Infrared (IR) spectra were recorded on a Nicolet 5700 FTIR spectrometer with ATR Smart Orbit Diamond adapter (Thermo Electron Corporation) and are reported as wave number (cm^{-1}). NMR spectra were recorded on a Varian VNMRS-600 spectrometer (^1H, 600 MHz and ^{13}C, 151 MHz) in $CDCl_3$ using TMS as the internal standard. TLC analysis was carried out using TLC Silica gel 60 F_{254} (aluminum sheets, Merck) and visualized by UV light or with permanganate solution followed by heating. Flash column chromatography was performed on Büchi system (Pump Manager C-615 and Fraction Collector C-660), using Normasil 60 silica gel (0.040–0.063 mm) (VWR). All solvents were dried and distilled according to conventional methods. THF, NMP, CH_2Cl_2, $CHCl_3$, toluene and acetonitrile were stored over molecular sieves and handled under inert atmosphere. All reagents were purchased from Sigma–Aldrich, Acros Organics, Alfa-Aesar, Merck or Mikrochem Trade and were used without further purification.

4.2. 1,3-Dipolar cycloaddition of nitrone 9 with phenylacetylene (10)

*4.2.1. Ethyl 2-benzyl-5-phenyl-2,3-dihydroisoxazole-3-carboxylate (**13**).* Nitrone **9** (1.5 g, 7.2 mmol) was mixed with anhydrous toluene (100 mL), phenylacetylene (**10**) (4.8 mL, 43.7 mmol, 6 equiv) was added and the mixture was stirred at 60 °C for 24 h under argon. Upon reaction completion (TLC, hexanes/EtOAc, 80:20), the solvent was evaporated in vacuo. The product was isolated by column chromatography (hexanes/EtOAc, 90:10) to give 2,3-dihydroisoxazole **13** (76%, 1.7 g, 5.5 mmol) as a pale yellow oil.

All spectroscopic data were in agreement with the literature.[7]

4.3. Bromination reactions

*4.3.1. 2-Benzyl-4-bromo-3,5-diphenyl-2,3-dihydroisoxazole (**15**).* The reaction flask was charged with 2,3-dihydroisoxazole **11** (0.5 g, 1.60 mmol), sealed with a rubber septum and filled with argon. Anhydrous THF (27 mL) was added and the solution was cooled to −40 °C. 2-Chloropyridine (0.45 mL, 4.8 mmol, 3 equiv) was added followed by dropwise addition of pyridinium tribromide (**14**) (0.63 g, 1.77 mmol, technical grade 90%, Sigma–Aldrich, 1.1 equiv) in anhydrous THF (5 mL) over 10 min. The reaction mixture was stirred for 24 h at −40 °C. Upon reaction completion, satd aq NH_4Cl solution was added and the reaction mixture was allowed to warm to ambient temperature. Water was added (30 mL), and the mixture was extracted with Et_2O (4×50 mL), combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 70:30) to provide 4-bromo-2,3-dihydroisoxazole **15** (53%, 0.33 g, 0.84 mmol) as a pale yellow powder. Mp 83–85 °C; IR (ATR): 3028, 2781, 1641, 1599, 1492, 1454, 1901, 1067, 1028, 737, 688, 643 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.90–7.87 (m, 2H), 7.42–7.39 (m, 5H), 7.35–7.28 (m, 8H), 4.98 (s, 1H), 4.46 (d, 1H, J=12.9 Hz), 4.15 (d, 1H, J=12.9 Hz); ^{13}C NMR (151 MHz, $CDCl_3$): δ=147.8, 139.3, 135.7, 129.7, 129.6, 128.6, 128.5, 128.3, 128.2, 127.8, 127.7 (2xC), 127.3, 88.4, 78.3, 63.5; HRMS (ESI): calcd for $C_{22}H_{19}Br^{79}NO$ $[M+H]^+$: 392.0650, found: 392.0642.

*4.3.2. 2-Benzyl-4-bromo-3-isopropyl-5-phenyl-2,3-dihydroisoxazole (**16**).* The reaction flask was charged with 2,3-dihydroisoxazole **12** (0.6 g, 2.15 mmol), sealed with a rubber septum and filled with argon. The substrate was dissolved in anhydrous THF (17 mL). Triethylamine (0.9 mL, 6.45 mmol, 3 equiv) was added, followed by dropwise addition of pyridinium tribromide (**14**) (1.53 g, 4.3 mmol, technical grade 90%, Sigma–Aldrich, 2 equiv) in anhydrous THF (5 mL) over 10 min. The reaction mixture was stirred for 5 h at ambient temperature. Upon reaction completion, satd aq NH_4Cl solution was added followed by the addition of water (30 mL) and the mixture was extracted with Et_2O (4x50 mL). Combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 70:30) to provide 4-bromo-2,3-dihydroisoxazole **16** (66%, 0.51 g, 1.42 mmol) as a yellow oil. IR (ATR): 3033, 2964, 1675, 1668, 1495, 1453, 1361, 1601, 1027, 739, 691, 674 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.85–7.78 (m, 2H), 7.44–7.30 (m, 8H), 4.30 (d, 1H, J=12.5 Hz), 3.87 (d, 1H, J=12.5 Hz), 3.82 (d, 1H, J=3.2 Hz), 2.04–1.94 (m, 1H), 0.91 (d, 3H, J=6.9 Hz), 0.83 (d, 3H, J=6.9 Hz); ^{13}C NMR (151 MHz, $CDCl_3$): δ=147.3, 135.9, 132.7, 129.9, 129.4, 128.3, 128.2, 127.7, 127.3, 87.0, 79.2, 64.4, 30.6, 19.0, 15.9; HRMS (ESI): calcd for $C_{19}H_{21}Br^{79}NO$ $[M+H]^+$: 358.0807, found: 358.0809.

*4.3.3. Ethyl 2-benzyl-4-bromo-5-phenyl-2,3-dihydroisoxazole-3-carboxylate (**17**).* The reaction flask was charged with 2,3-dihydroisoxazole **13** (0.5 g, 1.61 mmol), sealed with a rubber septum and filled with argon. The substrate was dissolved in anhydrous THF (11 mL). Triethylamine (0.67 mL, 4.83 mmol, 3 equiv) was added, followed by dropwise addition of pyridinium tribromide (**14**) (1.43 g, 4.03 mmol, technical grade 90%, Sigma–Aldrich, 2.5 equiv) in anhydrous THF (5 mL) over 10 min. The reaction mixture was stirred for 4 h at ambient temperature. Upon reaction completion, satd aq NH_4Cl solution was added followed by the addition of water and the mixture was extracted with Et_2O (4×50 mL). Combined organic layers were dried over $MgSO_4$ and

the solvent was evaporated in vacuo. The product was isolated by column chromatography (hexanes/CH_2Cl_2, 60:40) to provide 4-bromo-2,3-dihydroisoxazole **17** (50%, 0.31 g, 0.80 mmol) as a yellow oil. IR (ATR): 3138, 2887, 1722, 1669, 1594, 1449, 1290, 1238, 1191, 1018, 730, 690 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.87–7.83 (m, 2H), 7.42–7.31 (m, 8H), 4.58 (s, 1H), 4.43 (d, 1H, J=12.7 Hz), 4.22 (q, 2H, J=7.1 Hz), 4.07 (d, 1H, J=12.7 Hz), 1.26 (t, 3H, J=7.1 Hz); ^{13}C NMR (151 MHz, $CDCl_3$): δ=168.8, 149.8, 134.6, 130.0, 129.6, 128.6, 128.3, 128.1, 127.5, 127.1, 81.4, 76.0, 63.7, 61.8, 14.1; HRMS (ESI): calcd for $C_{19}H_{19}Br^{79}NO_3$ $[M+H]^+$: 388.0548, found: 388.0546.

4.4. Typical experimental procedure for bromine-lithium exchange

*4.4.1. 2-Benzyl-4-methyl-3,5-diphenyl-2,3-dihydroisoxazole (**19**).* A flame-dried reaction flask was flushed with argon and charged with 4-bromo-2,3-dihydoisoxazole **15** (200 mg, 0.51 mmol) dissolved in anhydrous THF (5 mL, 0.1 M). The solution was cooled to −80 °C and *n*-BuLi (0.31 mL, 0.77 mmol, 2.5 M in hexane, 1.5 equiv) was added dropwise over 15 min. Stirring was continued for 1 h at −80 °C. Thereafter, iodomethane (0.13 mL, 2.04 mmol, 4 equiv) was added by portions and the mixture was stirred for additional 24 h at −80 °C. The reaction was quenched by the addition of a satd aq NH_4Cl solution and the mixture was warmed to ambient temperature. Water (20 mL) was added to dissolve a formed slurry and the mixture was extracted with CH_2Cl_2 (3×20 mL). Combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The product was isolated by flash column chromatography (hexanes/CH_2Cl_2, 70:30) to give 2,3-dihydroisoxazole **19** (51%, 85 mg, 0.26 mmol) as a pale yellow oil. IR (ATR): 3060, 3028, 1695, 1668, 1599, 1495, 1449, 1232, 1068, 1026, 755, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.57–7.53 (m, 2H), 7.43–7.23 (m, 13H), 4.80–4.78 (m, 1H), 4.40 (d, 1H, J=13.0 Hz), 4.09 (d, 1H, J=13.0 Hz), 1.79 (d, 3H, J=1.1 Hz); ^{13}C NMR (151 MHz, $CDCl_3$): δ=145.9, 141.3, 136.9, 130.2, 129.9, 129.1, 128.9, 128.8, 128.7, 128.6, 128.0, 127.9, 127.7, 105.6, 79.5, 63.7, 11.1; HRMS (ESI): calcd for $C_{23}H_{22}NO$ $[M+H]^+$: 328.1701, found: 328.1680.

*4.4.2. (2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl) (phenyl) methanone (**20**).* Yield 61% (140 mg, 0.34 mmol) after flash column chromatography (hexanes/CH_2Cl_2, 50:50), colorless powder, Mp 94–96 °C; IR (ATR): 3030, 2875, 1608, 1596, 1575, 1347, 1135, 1074, 889, 737, 690, 672 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.46–7.01 (m, 20H), 5.62 (s, 1H), 4.48 (d, 1H, J=13.4 Hz), 4.30 (d, 1H, J=13.4 Hz); ^{13}C NMR (151 MHz, $CDCl_3$): δ=192.2, 162.0, 140.5, 138.5, 135.4, 131.5, 130.6, 129.5 (3×C), 128.9, 128.5 (3×C), 127.9, 127.8, 127.7, 127.4, 113.3, 75.9, 63.1; HRMS (ESI): calcd for $C_{29}H_{24}NO_2$ $[M+H]^+$: 418.1807, found: 418.1809.

*4.4.3. 1-(2-Benzyl-3,5-diphenyl-2,3-dihydroisoxazol-4-yl)-2-methylpropan-1-ol (**21**).* Yield 69% (140 mg, 0.36 mmol, single isomer) after flash column chromatography (hexanes/CH_2Cl_2, 70:30), colorless powder, Mp 75–77 °C; IR (ATR): 3566, 3432, 2954, 1678, 1599, 1493, 1454, 1027, 1004, 997, 762, 696 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ=7.68–7.65 (m, 2H), 7.43–7.25 (m, 13H), 4.94 (s, 1H), 4.44 (d, 1H, J=12.5 Hz), 4.11 (d, 1H, J=12.5 Hz), 4.07 (d, 1H, J=9.3 Hz), 1.85–1.77 (m, 1H), 0.99 (d, 3H, J=6.5 Hz), 0.89 (d, 3H, J=6.5 Hz), 0.86 (bs, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ=151.2, 142.7, 136.0, 129.6 (2xC), 129.4, 129.0, 128.5, 128.4 (2×C), 128.1, 127.6, 127.3, 110.9, 73.6, 73.3, 63.3, 33.4, 19.5, 19.2; HRMS (ESI): calcd for $C_{26}H_{28}NO_2$ for $[M+H]^+$: 386.2120, found: 386.2106.

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9. The ratios of 4-unsubstituted 2,3-dihydroisoxazole 11 determined from ^1H NMR spectra of the crude reaction mixtures: the reaction with iodomethane—18%; with benzoyl chloride—5%; with isobutyraldehyde—22%.