DOI: 10.1002/chem.201001461

A Versatile Iron-Catalyzed Protocol for the One-Pot Synthesis of Isoxazoles or Isoxazolines from the Same Propargylic Alcohols

Olivier Debleds, Eric Gayon, Emilie Ostaszuk, Emmanuel Vrancken,* and Jean-Marc Campagne*[a]

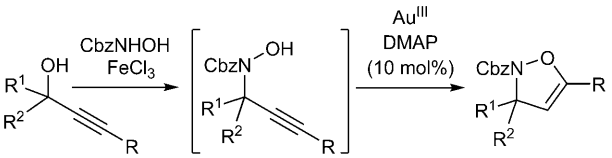
Abstract: The use *N*-sulfonyl-protected hydroxylamines as bi-nucleophiles in iron-catalyzed propargylic substitutions allows the selective one-pot synthesis of four classes of substituted isoxazoles or isoxazolines from the same propargylic alcohols (21 examples) by simply tuning the nature of the base. By using an iron(III) catalyst and a base such as triethylamine (3 equiv), isoxazoles **3** are obtained in good isolated yields (56–95%), whereas *N*-sulfonyl-protected isoxazolines **6** are selectively obtained (77–93% yield) by using iron and gold catalysts in the presence of a catalytic amount of pyridine (10 mol%).

Keywords: alkynes · cyclization · gold · heterocycles · iron

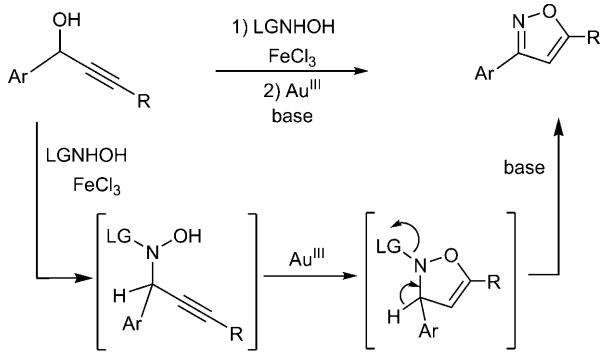
Introduction

The development of efficient, versatile, one-pot, multistep methodologies is of general interest for economic, environmental, and practical reasons. As part of a program aimed at developing gold- and iron-catalyzed reactions,[1] we recently described a concise, one-pot synthesis of 2,3-dihydroisoxazoles through a dual gold–iron-catalyzed condensation of an *N*-Cbz-protected hydroxylamine (Cbz = carbobenzyloxy) with propargylic alcohols.[2] In the first step, $FeCl_3$ promotes propargylic substitution[3,4] and subsequent addition of a combination of $NaAuCl_4 \cdot 2H_2O$ and 4-dimethylaminopyridine (DMAP) ensures the second cyclization step (Scheme 1).

The main features of this reaction are the ability to utilize an electron-withdrawing protecting group on the nitrogen atom and that the gold(III)-catalyzed cyclization process takes place second, in the presence of a base. Thus, we anticipated that, starting from substrates bearing a good leaving group on the nitrogen atom and in the presence of a stoichiometric amount of base, isoxazoles (Scheme 2) could be obtained in a one-pot, multistep sequence from propargylic alcohols. Because of their potential within medicinal chemistry, isoxazoles constitute an important class of heterocyclic compounds and, consequently, considerable effort has been focused on their synthesis.[5–8] Very recently, She et al.



Scheme 1. Selective access to isoxazolines (previous work)..



Scheme 2. Selective access to isoxazoles (this work). LG = leaving group.

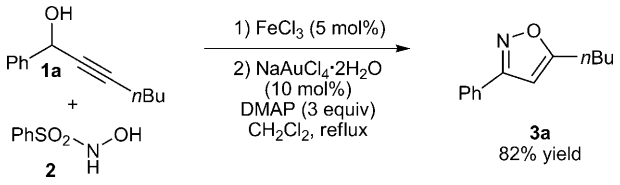
[a] Dr. O. Debleds, E. Gayon, E. Ostaszuk, Dr. E. Vrancken, Prof. J.-M. Campagne
Institut Charles Gerhardt
UMR 5253 CNRS-UM2-UM1ENSCM
8 rue de l'Ecole Normale
34296 Montpellier Cedex 5 (France)
Fax: (+33) 467144322
E-mail: emmanuel.vrancken@enscm.fr
jean-marc.campagne@enscm.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001461.

reported a regioselective one-pot route to 3,5-disubstituted isoxazoles based upon the conjugate addition of *N*-hydroxy-4-toluenesulfonamide to α-β-unsaturated ketones, followed by elimination of the tosyl (Ts) moiety, cyclization, and dehydration.[7] The concept of a one-pot procedure that uses readily available starting materials, as proposed by these authors, is of great interest, but up to seven equivalents of TsNHOH must be used to ensure good conversion and isolated yields are only moderate to good.

Results and Discussion

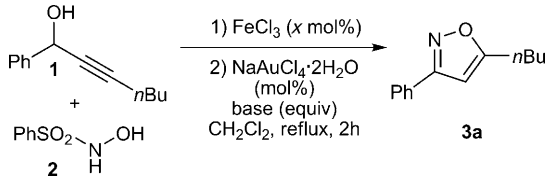
For our part, we decided to check the validity of our strategy of engaging *N*-sulfonyl-protected hydroxylamine as a bi-nucleophile in our dual gold–iron-catalyzed sequence. If a 1:1 mixture of model propargylic alcohol **1a** and *N*-hydroxybenzene sulfonamide **2** are treated with a catalytic amount of $FeCl_3$ (5 mol%), followed by the addition of $NaAuCl_4{\cdot}2H_2O$ (10 mol%) and DMAP (3 equiv), a clean reaction takes place to give the expected isoxazole, **3a**, in 82% isolated yield (Scheme 3).



Scheme 3. The one-pot synthesis of isoxazole **3a**.

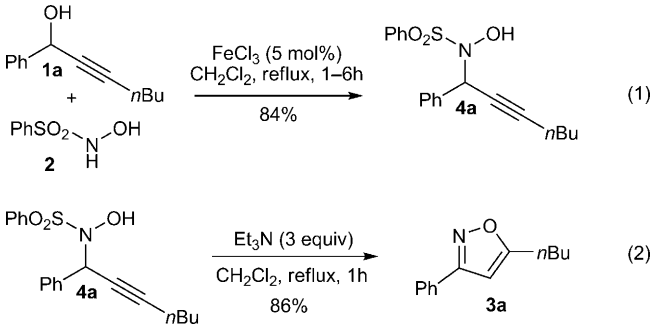
A study into the influence of different reaction parameters and, in particular, the nature of the base was then initiated (Table 1). The use of tertiary amines such as Et_3N ensures the formation of isoxazole **3a** in a similar yield to that with DMAP, despite the instantaneous formation of a gold mirror following the addition of $NaAuCl_4{\cdot}2H_2O$ (Table 1, entry 2). The role of gold was, therefore, questioned and a control reaction was performed without the gold catalyst, in the presence of Et_3N (3 equiv). Under these conditions, **3a** was obtained in an improved yield (90%, Table 1, entry 3). In contrast, the reaction conducted in the absence of both the base and the gold catalyst stops at the propargylic substitution step and gives **4a** in an 84% yield [Eq. (1)]. Starting from isolated (and purified) propargyl hydroxylamine **4a**, isoxazole **3a** can then be obtained in 86% yield, in refluxing CH_2Cl_2, in the presence of Et_3N (3 equiv) [Eq. (2)].

Table 1. Optimization of the reaction conditions for the one-pot synthesis of isoxazoles.

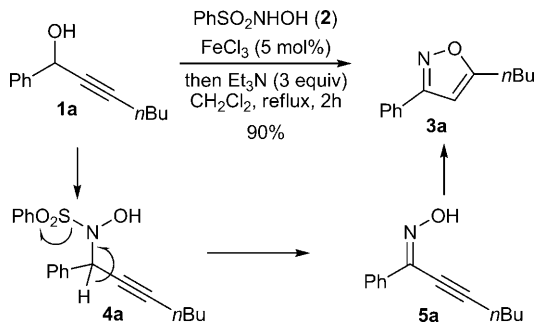


Entry	$FeCl_3$ [mol%]	$NaAuCl_4{\cdot}2H_2O$ [mol%]	Base ([equiv])	Yield[a] [%]
1	5	10	DMAP (3)	82
2	5	10	Et_3N (3)	80
3	5	–	Et_3N (3)	90
4	2.5	–	Et_3N (3)	89
5	2.5	–	Et_3N (1.5)	83

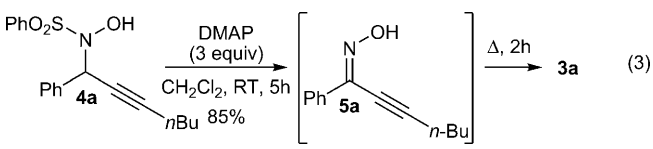
[a] Isolated yield.



These experiments suggest the following reaction sequence: an iron-catalyzed propargylic substitution, followed by a base induced β-elimination of the sulfone moiety and then cyclization of transient oxime derivative **5a** (Scheme 4).[9] Indeed, if **4a** is treated with DMAP (3 equivalents) at room temperature, a clean elimination takes place (by ^1H NMR spectrum monitoring) to give oxime **5a**,[10] which subsequently leads to isoxazole **3a** after heating to reflux [Eq. (3)].[11]



Scheme 4. A probable reaction pathway for the iron-catalyzed isoxazole synthesis.

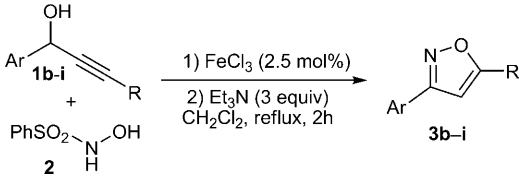


During the preparation of this manuscript, Perumal et al. described a gold-catalyzed isoxazole synthesis from isolated propargylic oximes.[8] It is worth noting that in our reaction conditions, a cleaner crude mixture and better yields are observed in the absence of gold (see Table 1, entries 1–3). Op-

timization of the reaction conditions gave the following results: the amount of iron catalyst can be reduced to 2.5 mol% and still maintain a high yield (89%; Table 1, entry 4), but moving to 1.5 equivalents of Et_3N induced a slightly lower yield (83%; Table 1, entry 5).

The scope of the isoxazole formation was then extended to various propargylic alcohols by using the optimized reaction conditions described in Table 1, entry 4. In most cases, the reactions proceed cleanly and the expected isoxazoles **3b–g** are obtained in good to excellent yields, whatever the nature (alkyl or aryl) and steric hindrance (primary, secondary, or tertiary alkyl) at the acetylenic position of **1b–i** (Table 2). Bromine in the *para* position of an propargylic

Table 2. Scope of the one-pot synthesis of isoxazoles.



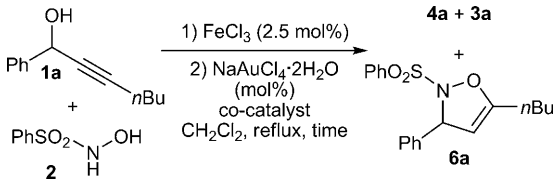
Entry	Ar	R	Product	Yield[a] [%]
1	Ph	*t*Bu	**3b**	93
2	Ph	*c*Pr[b]	**3c**	87
3	Ph	*i*Pr	**3d**	94
4	Ph	Ph	**3e**	84
5	4-FC_6H_4	*n*Bu	**3f**	95
6	4-BrC_6H_4	*n*Bu	**3g**	91
7	4-$MeOC_6H_4$	*n*Bu	**3h**	77
8	thiophen-2-yl	*n*Bu	**3i**	56

[a] Isolated yield. [b] *c*Pr = cyclopropyl.

aryl group, which potentially allows further functionalization of the aromatic ring, is well tolerated, as shown for **3g**, isolated in an excellent 91% yield (Table 2, entry 6). Lower yields are obtained by using alcohols **1h** and **i**, containing electron-rich aromatic groups in the propargylic position (Ar = thiophen-2-yl or 4-$MeOC_6H_4$, Table 2, entries 7 and 8).

We have previously shown that a catalytic amount of base favors the gold-assisted cyclization of *N*-Cbz analogues of **4** to form isoxazolines [Eq. (1), Scheme 1, and reference [2]]. Here, the *N*-sulfonyl-substituted derivatives exhibit the same behavior: a poor 32% yield of **6a** is obtained if $NaAuCl_4{\cdot}2H_2O$ is used without a base as co-catalyst (Table 3, entries 1 and 2). The presence of DMAP in the reaction mixture helps the cyclization process, but induces the formation of isoxazole **3a** as a side product (Table 3, entry 3). Notably, the isolated yield of **6a** in this case is significantly higher than that without the base co-catalyst, which suggests that the gold-cyclization pathway is faster than the oxime formation. A decrease in the amount of base has a beneficial effect upon both the yield of **6a** and the selectivity for it, but the undesired isoxazole, **3a**, is still present in the crude mixture (Table 3, entries 4 and 5). The development of a selective route to access **6a** requires a subtle choice of the base. Indeed, a highly selective and efficient

Table 3. Optimization of the reaction conditions for the one-pot synthesis of isoxazolines.



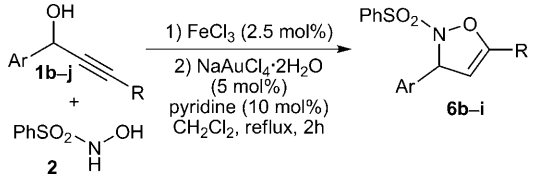
Entry	$NaAuCl_4$ [mol%]	Co-catalyst ([mol%])	*t* [h]	**4a**:**3a**:**6a**[a]	Yield[b] [%]
1	–	–	6	100:0:0	–
2	5	–	4	63:0:37	32
3	5	DMAP (30)	2	0:27:73	51
4	5	DMAP (10)	2	0:8:92	81
5	5	Et_3N (10)	2	0:9:91	80
6	5	pyridine (10)	2	0:0:100	87

[a] Determined by ^1H NMR spectroscopy of the crude product. [b] Isolated yield.

reaction takes place in the presence of pyridine, **6a** being obtained as the only product in a good yield (87%; Table 3, entry 6)

This procedure can be efficiently extended to various analogues of **1a**, as illustrated in the Table 4. Bulky substituents in the acetylenic position are well tolerated, as well as electron-donating or electron-withdrawing groups on the aromatic ring.

Table 4. Scope of the one-pot synthesis of isoxazolines.

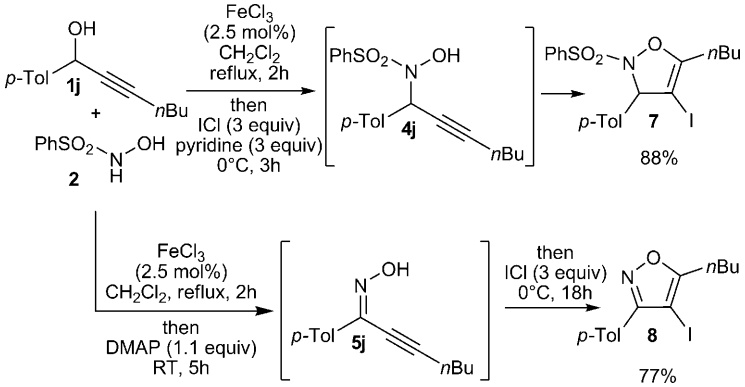


Entry	Ar	R	Product	Yield[a] [%]
1	Ph	*t*Bu	**6b**	77
2	Ph	*c*Pr	**6c**	86
3	Ph	*i*Pr	**6d**	87
4	Ph	Ph	**6e**	93
5	4-FC_6H_4	*n*Bu	**6f**	89
6	4-BrC_6H_4	*n*Bu	**6g**	87
7	4-$MeOC_6H_4$	*n*Bu	**6h**	81
8	thiophen-2-yl	*n*Bu	**6i**	83
9	4-MeC_6H_4	*n*Bu	**6j**	89

[a] Isolated yield.

Starting from readily available propargylic alcohols, iron-catalyzed propargylic substitutions with *N*-hydroxy-4-toluenesulfonamide allow, by a judicious choice of reaction conditions, efficient, versatile access to propargylic hydroxylamines **4** or propargylic oximes **5** (by adding a base to the reaction mixture). From these compounds, alternative modes of cyclization can be envisioned. Larock et al. recently reported the electrophilic cyclization of *O*-methyl oximes,[6b] allowing elegant access to functionalized isoxazoles such as

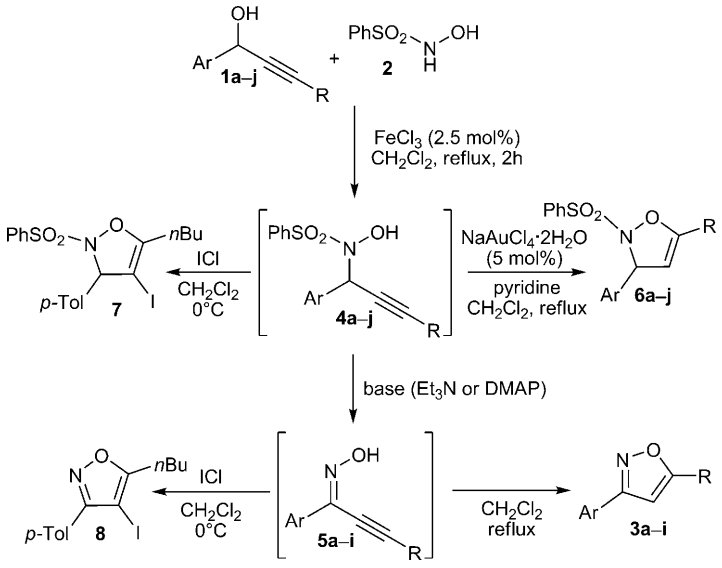
valdecoxib.[6c] Inspired by this work, compounds **7** and **8** where obtained from **1j** through the iodo cyclization of transient intermediates **4j** and **5j**, in a one-pot sequence, in 88 and 77% isolated yields, respectively (Scheme 5).



Scheme 5. Versatile routes to iodoisoxazoline **7** or iodoisoxazole **8** in a one-pot sequence from the same propargylic alcohol, **1j**.

Conclusion

In conclusion, the use of *N*-sulfonyl-protected hydroxylamines as bi-nucleophiles in iron-catalyzed propargylic substitutions allows the selective, in situ formation of propargylic hydroxylamines or propargylic oximes from the same starting propargylic alcohols. Simple tuning of the cyclization conditions gives a practical and efficient one-pot route to various functionalized heterocycles (21 examples, Scheme 6).



Scheme 6. Versatile routes to various substituted heterocycles from the same propargylic alcohols **1a–j**. *p*-Tol = *para*-tolyl.

Experimental Section

General considerations: Unless otherwise stated all commercial materials were used without further purification. Reactions were carried out in round-bottomed flasks equipped with a magnetic stirring bar. Dichloromethane was distilled over CaH_2. TLC analysis of all reactions was performed on silica gel 60 F_{254} TLC plates. Chromatography was carried out with silica gel 60 A (35–70 μm). FT-IR spectra were recorded with a Perkin Elem Spectrum 1000. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Ultra shield 400 plus and referenced to $CDCl_3$, unless otherwise noted. Mass spectra and high-resolution mass spectra were obtained from the mass spectrometer operated by the Centre Commun de Spectrométrie de Masse of the University Claude Bernard Lyon 1 and the Laboratoire de Mesure Physique of the University Montpellier 2.

General procedure A—the preparation of isoxazoles (3a–i): *N*-Benzenesulfonamide hydroxylamine (0.8 mmol) and iron(III) chloride (0.02 mmol) were added to a solution of propargylic alcohol (1 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 1.5 h at reflux and then triethylamine (TEA; 3.0 mmol) was added. The resulting reaction mixture was stirred for an additional 3 h at reflux. Upon completion (^{1}H NMR spectrum monitoring), the reaction was filtered through Celite and concentrated in vacuo. Purification of the crude material by chromatography through silica gel (cyclohexane/diethyl ether) afforded the expected product.

5-Butyl-3-phenylisoxazole (3a): By following general procedure A, compound **3a** was obtained in 90% yield as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.4$ Hz, 3H), 1.39–1.48 (m, 2H), 1.69–1.77 (m, 2H), 2.80 (t, $J = 7.6$ Hz, 2H), 6.28 (s, 1H), 7.41–7.47 (m, 3H), 7.78–7.8 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$, 22.1, 26.4, 29.5, 98.7, 126.7 (2C), 128.8 (2C), 129.4, 129.7, 162.2, 174.2 ppm; these spectral data are consistent with those in the literature.[12]

5-*tert*-Butyl-3-phenylisoxazole (3b): By following general procedure A, compound **3b** was obtained in 93% yield as a white solid. M.p. 41°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.4$ (s, 9H), 6.24 (s, 1H), 7.42–7.46 (m, 3H), 7.78–7.8 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.8$, 32.8, 96.3, 126.7 (2C), 128.7 (2C), 129.5, 129.7, 162.0, 181.7 ppm; MS (EI): *m/z* (%): 201 (37) $[M]^+$, 186 (18), 144 (100), 116 (11), 77 (16); IR (FT-IR): $\tilde{\nu} = 3061$, 2966, 2878, 1598, 1576, 1480, 1465, 1443, 1402, 1365, 1277, 1030, 982, 919, 801, 768, 698 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{13}H_{15}NO+H]^+$: 202.1232; found: 202.1227.

5-Cyclopropyl-3-phenylisoxazole (3c): By following general procedure A, compound **3c** was obtained in 87% yield as a white solid. M.p. 45°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.00$–1.11 (m, 4H), 2.08 (tt, $J = 5.1$, 8.4 Hz, 1H), 6.21 (s, 1H), 7.41–7.46 (m, 3H), 7.75–7.79 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.1$, 8.3 (2C), 96.8, 126.6 (2C), 128.7 (2C), 129.3, 129.7, 162.4, 175.2 ppm; MS (EI): *m/z* (%): 185 (100) $[M]^+$, 170 (17), 156 (25), 144 (94), 117 (28), 89 (12), 77 (46); IR (FT-IR): $\tilde{\nu} =$ 3121, 3062, 3018, 1605, 1583, 1469, 1447, 1410, 1365, 1284, 1026, 993, 768, 691 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{12}H_{11}NO+H]^+$: 186.0919; found: 186.0913.

5-Isopropyl-3-phenylisoxazole (3d): By following general procedure A, compound **3d** was obtained in 94% yield as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.35$ (s, 3H), 1.37 (s, 3H), 3.13 (d sept, $J = 0.7$, 7.0 Hz, 1H), 6.27 (d, $J = 0.8$ Hz, 1H), 7.41–7.45 (m, 3H), 7.78–7.80 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.8$ (2C), 27.2, 97.0, 126.7 (2C), 128.7 (2C), 129.4, 129.7, 162.1, 179.2 ppm; MS (ESI+): *m/z* (%): 187 (32) $[M]^+$, 144 (100), 116 (14), 77 (18); IR (FT-IR): $\tilde{\nu} = 3062$, 2966, 2929, 2878, 1601, 1572, 1476, 1439, 1410, 1340, 1181, 986, 912, 768, 694 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{12}H_{13}NO+H]^+$: 188.1075; found: 188.1070.

3,5-Biphenylisoxazole (3e): By following general procedure A, compound **3e** was obtained in 84% yield as a white solid. M.p. 137°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.84$ (s, 1H), 7.46 –7.51 (m, 6H), 7.84–7.89 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 97.4$, 125.8 (2C), 126.8 (2C), 127.4, 128.9 (2C), 129.0 (2C), 129.1, 130.0, 130.2, 162.9, 170.4 ppm; MS (EI): *m/z* (%): 221 (84) $[M]^+$, 193 (8), 144 (18), 105 (100), 77 (52), 51 (14); IR (FT-IR): $\tilde{\nu} = 3114$, 3062, 2981, 1612, 1594, 1568,

1485, 1450, 1402, 1266, 1078, 952, 916, 816, 739, 698, 529 cm^{-1}; HRMS (EI): *m/z* calcd for $[C_{15}H_{11}NO]$: 221.0841; found: 221.0840.

5-Butyl-3-(4-fluorophenyl)isoxazole (3f): By following general procedure A, compound **3f** was obtained in 95% yield as a pale-yellow solid. M.p. 35°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 1H), 1.38–1.47 (m, 2H), 1.68–1.76 (m, 2H), 2.78 (t, J = 7.6 Hz, 2H), 6.24 (s, 1H), 7.10–7.14 (m, 2H), 7.76–7.79 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 22.1, 26.4, 29.5, 98.6, 116.0 (d, J(C,F) = 22 Hz, 2C), 125.7 (d, J(C,F) = 3.4 Hz, 1C), 128.6 (d, J(C,F) = 8.6 Hz, 2C), 161.4, 162.4, 164.9, 174.5 ppm; MS (EI): *m/z* (%): 219 (68) $[M]^+$, 190 (11), 177 (64), 162 (100), 135 (78), 107 (16), 95 (20); IR (FT-IR): $\tilde{\nu}$ = 3114, 3077, 2929, 2966, 2878, 1612, 1587, 1524, 1461, 1435, 1384, 1233, 1163, 949, 842, 599, 525 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{13}H_{14}FNO+H]^+$: 220.1138; found: 220.1125.

3-(4-Bromophenyl)-5-butylisoxazole (3g): By following general procedure A, compound **3g** was obtained in 91% yield as a pale-yellow solid. M.p. 67°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3H), 1.37–1.46 (m, 2H), 1.67–1.75 (m, 2H), 2.78 (t, J = 7.6 Hz), 6.25 (s, 1H), 7.54–7.57 (m, 2H), 7.63–7.67 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 22.2, 26.5, 29.6, 98.6, 124.0, 128.2 (2C), 128.4, 132.0 (2C), 161.4, 174.6 ppm; MS (EI): *m/z* (%): 281 (96) $[M+2]^+$, 279 (95) $[M]^+$, 237 (79), 224 (100), 222 (98), 197 (79), 195 (78), 157 (23), 115 (13), 102 (11), 75 (19); IR (FT-IR): $\tilde{\nu}$ = 3114, 3077, 2959, 2929, 2863, 1605, 1568, 1505, 1458, 1428, 1384, 1074, 1008, 952, 835, 790 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{13}H_{14}BrNO+H]^+$: 280.0337; found: 280.0330.

5-Butyl-3-(4-methoxyphenyl)isoxazole (3h): By following general procedure A, compound **3h** was obtained in 77% yield as a pale-yellow solid. M.p. 28°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 7.4 Hz, 1H), 1.38–1.47 (m, 2H), 1.68–1.76 (m, 2H), 2.77 (t, J = 7.6 Hz, 2H), 3.84 (s, 3H), 6.22 (s, 1H), 6.94–6.97 (m, 2H), 7.71–7.73 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 22.1, 26.4, 29.5, 55.3, 98.5, 114.1 (2C), 121.9, 128.0 (2C), 160.7, 161.9, 173.9 ppm; MS (EI): *m/z* (%): 231 (100) $[M]^+$, 189 (58), 174 (87), 146 (53), 132 (14), 92 (9), 77 (13); IR (FT-IR): $\tilde{\nu}$ = 3003, 2959, 2937, 2870, 1616, 1572, 1531, 1509, 1465, 1432, 1399, 1299, 1255, 1177, 1034, 912, 835, 801, 599, 532 cm^{-1}; HRMS (EI): *m/z* calcd for $[C_{14}H_{17}NO_2]$: 231.1259; found: 231.1256.

5-Butyl-3-(thiophen-2-yl)isoxazole (3i): By following general procedure A, compound **3i** was obtained in 56% yield as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, J = 7.4 Hz, 3H), 1.72–1.81 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 6.22 (s, 1H), 7.10 (dd, J = 3.6, 5.0 Hz, 1H), 7.39 (dd, J = 1.1, 5.1 Hz, 1H), 7.43 ppm (dd, J = 1.1, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 20.8, 28.6, 98.9, 127.0, 127.2, 127.5, 131.2, 157.4, 174.0 ppm; MS (EI): *m/z* (%): 193 (100) $[M]^+$, 165 (15), 150 (88), 123 (36), 110 (6), 95 (7), 71 (8); IR (FT-IR): $\tilde{\nu}$ = 3114, 3091, 2966 2929, 2870 1601, 1548, 1461, 1435, 1395, 1229, 912, 857, 787, 709 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{11}H_{13}NOS+H]^+$: 194.0640; found: 194.0638.

***N*-Hydroxy-*N*-(1-phenylhept-2-ynyl)benzenesulfonamide (4a)**: *N*-Hydroxybenzenesulfonamide (1.2 mmol) and $FeCl_3$ (0.1 mmol) were added to a solution of propargylic alcohol (1 mmol) in dichloromethane (5 mL). The mixture was refluxed for 1 h. Upon completion, the reaction was filtered through Celite, concentrated in vacuo, and the crude material loaded onto a silica gel column and purified by chromatography. Compound **4a** was obtained in 84% yield as a white solid. M.p. 99°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.4 Hz, 3H), 1.25–1.29 (m, 4H), 1.83–1.86 (m, 2H), 5.84 (s, 1H), 6.54 (brs, 1H), 7.32–7.39 (m, 3H), 7.55–7.69 (m, 5H), 8.01–8.03 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 18.1, 21.7, 30.1, 56.7, 71.7, 89.9, 128.0, 128.1 (2C), 128.2 (2C), 128.3 (2C), 129.8 (2C), 133.4, 134.7, 136.3 ppm; MS (ES+): *m/z* (%): 687 (21) $[2M<M+>H]^+$, 344 (19) $[M+H]^+$, 326 (6), 214 (8), 171 (11); IR (FT-IR): $\tilde{\nu}$ = 3380, 3064, 2957, 2931 2871, 1448, 1353, 1169, 1090, 755, 733, 686, 607, 571 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{19}H_{21}NO_3S+H]^+$: 344.1320; found: 344.1314.

General procedure B—the preparation of isoxazolines (6a–j): *N*-Hydroxybenzenesulfonamide (1 mmol) and $FeCl_3$ (0.025 mmol) were added to a solution of propargylic alcohol (1.2 mmol) in CH_2Cl_2 (5 mL). The mixture was refluxed for 1 h, then $NaAuCl_4{\cdot}2H_2O$ (0.05 mmol) and pyridine (0.1 mmol) were added and reflux was maintained for an additional 2 h. After reaction completion (TLC monitoring), the mixture was concentrated in vacuo and the crude material loaded onto a silica gel column and purified by chromatography.

5-Butyl-3-phenyl-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6a): By following general procedure B, compound **6a** was obtained in 87% yield as a pale-yellow solid. M.p. 78°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.21 Hz, 3H), 1.22–1.40 (m, 4H), 1.96–2.12 (m, 2H), 4.53 (s, 1H), 5.79 (s, 1H), 7.30–7.37 (m, 5H), 7.56–7.60 (m, 2H), 7.69–7.72 (m, 1H), 8.02–8.06 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 22.1, 25.2, 28.3, 69.1, 95.9, 127.05 (2C), 128.32, 128.71 (2C), 128.93 (2C), 129.43 (2C), 133.9, 134.1, 139.87, 156.44 ppm; MS (ESI+): *m/z* (%): 344 (88) $[M+H]^+$, 308 (12), 288 (15), 254 (60), 218 (33), 202 (23) $[M-PhSO_2]^+$, 171 (24), 147 (43), 92 (41), 90 (100); IR (FT-IR): $\tilde{\nu}$ = 3063, 2957, 2931, 2871, 1686, 1494, 1364, 1311, 1172, 1088, 1027, 925, 847, 755, 728, 697, 645, 580, 561 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{19}H_{21}NO_3S+H]^+$: 344.1320; found: 344.1337.

5-*tert*-Butyl-3-phenyl-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6b): By following general procedure B, compound **6b** was obtained in 77% yield as a white solid. M.p. 129°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 9H), 4.60 (d, J = 2.4 Hz, 1H), 5.90 (d, J = 2.4 Hz, 1H), 7.30–7.39 (m, 5H), 7.54–7.58 (m, 2H), 7.66–7.70 (m, 1H), 8.0–8.02 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0, 31.4, 68.7, 94.0, 127.08 (2C), 128.3, 128.7 (2C), 128.9 (2C), 129.6 (2C), 134.0, 134.5, 140.2, 163.9 ppm; MS (ESI−): *m/z* (%): 342 (24) $[M-H]^-$, 324 (100), 260 (23), 227 (22), 141 (17); MS (ESI+): *m/z* (%): 687 (66) $[2M+H]^+$, 345 (47) $[M+2H]^{2+}$, 344 (100) $[M+H]^+$, 260 (32), 220 (77); IR (FT-IR): $\tilde{\nu}$ = 3062, 3021, 2966, 2907, 2863, 1701, 1675, 1598, 1480, 1450, 1362, 1170, 1089, 912, 757, 731, 687, 573 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{19}H_{21}NO_3S+H]^+$: 344.1320; found: 344.1318.

5-Cyclopropyl-3-phenyl-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6c): By following general procedure B, compound **6c** was obtained in 86% yield as a white solid. M.p. 78°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.46–0.52 (m, 1H), 0.59–0.64 (m, 1H), 0.66–0.79 (m, 2H), 1.31–1.38 (m, 1H), 4.51 (dd, J = 0.6, 2.5 Hz, 1H), 5.80 (d, J = 2.4 Hz, 1H), 7.29–7.38 (m, 5H), 7.55–7.59 (m, 2H), 7.68–7.71 (m, 1H), 8.00–8.02 ppm (m, 2H); ^{13} CNMR (100 MHz, $CDCl_3$): δ = 5.8, 6.2, 6.4, 69.2, 94.3, 127.0 (2C), 128.3, 128.7 (2C), 128.9 (2C), 129.4 (2C), 134.1, 137.0, 139.9, 157.6 ppm; MS (ESI+): *m/z* (%): 655 (40) $[2M+H]^+$, 328 (100) $[M+H]^+$, 242 (9), 146 (13); IR (FT-IR): $\tilde{\nu}$ = 3084, 3062, 3011, 2974, 2937, 2892, 1686, 1594, 1487, 1443, 1358, 1314, 1170, 1089, 1056, 927, 753, 728, 694, 562 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{18}H_{17}NO_3S+H]^+$: 328.1007; found: 328.1007.

5-Isopropyl-3-phenyl-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6d): By following general procedure B, compound **6d** was obtained in 87% yield as a white solid. M.p. 109°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 2.32–2.39 (m, 1H), 4.54 (dd, J = 1.1, 2.4 Hz, 1H), 5.83 (dd, J = 1.6, 2.3 Hz, 1H), 7.30–7.39 (m, 5H), 7.54–7.57 (m, 2H), 7.66–7.68 (m, 1H), 8.00–8.02 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, 20.2, 25.9, 68.9, 94.4, 127.0 (2C), 128.3 (C_9), 128.7 (2C), 128.9 (2C), 129.5 (2C), 134.0, 134.2, 139.9, 161.6 ppm; MS (ESI+): *m/z* (%): 659 (72) $[2M+H]^+$, 330 (100) $[M+H]^+$, 260 (4), 186 (13); IR (FT-IR): $\tilde{\nu}$ = 3070, 3025, 2981, 2922, 2885, 1679, 1447, 1365, 1170, 1093, 1070, 1030, 916, 757, 728, 694, 643, 595, 573 cm^{-1}; HRMS (ESI+): *m/z* calcd for $[C_{18}H_{19}NO_3S+H]^+$: 330.1164; found: 330.1158.

3,5-Diphenyl-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6e): By following general procedure B, compound **6e** was obtained in 93% yield as a white solid. M.p. 138°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.19 (d, J = 2.8 Hz, 1H), 5.96 (d, J = 2.8 Hz, 1H), 7.33–7.44 (m, 12H), 7.56–7.60 (m, 1H), 7.99–8.02 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.0, 69.8, 125.5 (2C), 126.6, 127.1 (2C), 128.4 (2C), 128.5, 128.8 (2C), 128.9 (2C), 129.2 (2C), 129.7, 133.6, 134.2, 139.2, 153.6 ppm; MS (ES+): *m/z* (%): 727 (33) $[2M+H]^+$, 364 (100) $[M+H]^+$; IR (FT-IR): $\tilde{\nu}$ = 3121, 3062, 3018, 1668, 1583, 1494, 1450, 1365, 1170, 1089, 1015, 886, 757, 728, 691, 647, 610, 576 cm^{-1}; HRMS (ES+): *m/z* calcd for $[C_{21}H_{17}NO_3S+H]^+$: 364.1007; found: 364.1004.

5-Butyl-3-(4-fluorophenyl)-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6f): By following general procedure B, compound **6f** was obtained in 89% yield as a white solid. M.p. 76°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.2 Hz, 3H), 1.22–1.42 (m, 4H), 1.96–2.12 (m, 2H), 4.52 (td, J =

1.2, 2.2 Hz, 1H), 5.78 (d, J=1.2 Hz, 1H), 7.01–7.06 (m, 2H), 7.31–7.35 (m, 2H), 7.54–7.58 (m, 2H), 7.67–7.71 (m, 1H), 7.98–8.02 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.6, 22.1, 25.1, 28.3, 68.4, 95.6, 115.5 (d, J(C,F)=21.5 Hz, 2C), 128.8 (d, J(C,F)=8.9 Hz, 2C), 128.9 (2C), 129.4 (2C), 133.9, 134.1, 135.7 (d, J(C,F)=3.0 Hz, 1C), 156.7, 161.4, 163.9 ppm; MS (ESI+): m/z (%): 723 (78) $[2M+H]^+$, 362 (100) $[M+H]^+$, 188 (13); IR (FT-IR): $\tilde{\nu}$=3121, 3070, 2959, 2937, 2863, 1686, 1605, 1502, 1450, 1365, 1222, 1174, 1089, 1015, 901, 838, 753, 735, 691, 643, 580 cm^{-1}; HRMS (ESI+): m/z calcd for $[C_{19}H_{20}FNO_3S+H]^+$: 362.1226; found: 362.1213.

3-(4-Bromophenyl)-5-butyl-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6g): By following general procedure B, compound **6g** was obtained in 87% yield as a pale-yellow solid. M.p. 117°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (t, J=7.2 Hz, 3H), 1.21–1.39 (m, 4H), 1.96–2.11 (m, 2H), 4.51 (td, J=1.1, 2.3 Hz, 1H), 5.75 (d, J=1.2 Hz, 1H), 7.22–7.26 (m, 2H), 7.47–7.49 (m, 2H), 7.54–7.58 (m, 2H), 7.67–7.71 (m, 1H), 7.98–8.02 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.6, 22.1, 25.1, 28.3, 68.4, 95.4, 122.3, 128.7 (2C), 128.9 (2C), 129.4 (2C), 131.8 (2C), 133.9, 134.2, 139.0, 156.9 ppm; MS (ESI+): m/z (%): 845 (47) $[2M+H]^+$, 424 (62, $[M+H]^+$, ^{81}Br), 422 (63, $[M+H]^+$, ^{79}Br), 188 (100); IR (FT-IR): $\tilde{\nu}$=3114, 3070, 2959, 2929, 2870, 1682, 1483, 1443, 1362, 1166, 1085, 1011, 905, 827, 731, 683, 632, 584, 554 cm^{-1}; HRMS (ESI+): m/z calcd for $[C_{19}H_{20}BrNO_3S+H]^+$: 422.0426; found: 422.0426.

5-Butyl-3-(4-methoxyphenyl)-2-(phenylsulfonyl)-2,3-dihydroisoxazole (6h): By following general procedure B, compound **6h** was obtained in 81% yield as a pale-yellow solid. M.p. 96°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (t, J=7.2 Hz, 3H), 1.22–1.40 (m, 4H), 1.96–2.12 (m, 2H), 3.80 (s, 3H), 4.50 (td, J=1.1, 2.1 Hz, 1H), 5.76 (d, J=1.2 Hz, 1H), 6.87–6.91 (m, 2H), 7.26–7.30 (m, 2H), 7.53–7.58 (m, 2H), 7.66–7.71 (m, 1H), .799–8.03 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.6, 22.1, 25.2, 28.4, 55.3, 68.8, 95.9, 114.0 (2C), 128.7 (2C), 128.9 (2C), 129.4 (2C), 131.9, 134.0, 134.1, 156.3, 159.6 ppm; MS (ESI−): m/z (%): 372 (100) $[M-H]^-$, 324 (26), 227 (23), 157 (10), 141 (16); MS (ESI+): m/z (%): 747 (47) $[2M+H]^+$, 375 (50) $[M+2H]^{2+}$, 374 (100) $[M+H]^+$, 220 (82); IR (FT-IR): $\tilde{\nu}$=3062, 2959, 2937, 2878, 2833, 1686, 1609, 1583, 1509, 1450, 1362, 1306, 1251, 1174, 1089, 1030, 838, 757, 731, 691, 643, 584, 558 cm^{-1}; HRMS (ESI+): m/z calcd for $[C_{20}H_{23}NO_4S+H]^+$: 374.1426; found: 374.1425.

2-(Phenylsulfonyl)-5-propyl-3-(thiophen-2-yl)-2,3-dihydroisoxazole (6i): By following general procedure B, compound **6i** was obtained in 83% yield as a purple oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.87 (t, J=7.4 Hz, 3H), 1.44 (sext, J=7.4 Hz, 2H), 1.95–2.01 (m, 2H), 4.61 (td, J=1.0, 2.1 Hz, 1H), 6.09 (d, J=1.8 Hz, 1H), 6.99 (dd, J=3.5, 5.1 Hz, 1H), 7.09 (d, J=3.5 Hz, 1H), 7.29 (dd, J=1.2, 5.1 Hz, 1H), 7.53–7.57 (m, 2H), 7.66–7.70 (m, 1H), 7.96–8.00 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.5, 19.6, 27.4, 64.5, 95.7, 125.6, 126.2, 127.1, 128.9 (2C), 129.4 (2C), 134.1, 134.2, 144.1, 157.2 ppm; MS (ESI−): m/z (%): 334 (100) $[M-H]^-$, 286 (9), 241 (18), 192 (22); MS (ESI+): m/z (%): 671 (21) $[2M+H]^+$, 336 (100) $[M+H]^+$, 230 (7), 194 (24); IR (FT-IR): $\tilde{\nu}$=3114, 3070, 2966, 2929, 2870, 1686, 1579, 1450, 1365, 1314, 1174, 1089, 1019, 916, 764, 724, 691, 650, 599, 565 cm^{-1}; HRMS (ESI−) m/z calcd for $[C_{16}H_{17}NO_3S_2-H]^+$: 334.0572; found: 334.0576.

5-Butyl-2-(phenylsulfonyl)-3-*para*-tolyl-2,3-dihydroisoxazole (6j): By following general procedure B, compound **6j** was obtained in 89% yield as a pale-yellow solid. M.p. 83°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.86 (t, J=7.2 Hz, 3H; CH_3 *n*Bu), 1.21–1.41 (m, 4H; CH_2 *n*Bu), 1.95–2.12 (m, 2H; CH_2 *n*Bu), 2.34 (s, 3H; CH_3Ar), 4.51–4.54 (m, 1H), 5.76–5.79 (m, 1H), 7.17 (d, J=8.0 Hz, 2H; Ar), 7.26 (d, J=8.0 Hz, 2H; Ar), 7.56–7.60 (m, 2H; Ar), 7.66–7.71 (m, 1H; Ar), 7.99–8.03 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 21.1, 22.1, 25.2, 28.4, 69.0, 96.0, 127.0 (2C), 128.9 (2C), 129.3 (2C), 129.4 (2C), 134.1, 137.0, 138.2, 156.3 ppm; MS (ESI+): m/z (%): 733 (10), 716 (35) $[2M+H]^+$, 460 (20), 358 (100) $[M+H]^+$, 185 (5); IR (KBr): $\tilde{\nu}$=2977, 2933, 2863, 1446, 1382, 1350, 1123, 1077, 934, 845, 727, 610 cm^{-1}; HRMS (ESI+): m/z calcd for $[C_{20}H_{23}NO_3S]$: 358.1469; found: 358.1477.

5-Butyl-4-iodo-2-(phenylsulfonyl)-3-*para*-tolyl-2,3-dihydroisoxazole (7): *N*-hydroxybenzenesulfonamide (728 mg, 4.12 mmol, 1 equiv) and $FeCl_3$ (17 mg, 0.103 mmol, 2.5% mol) were added to a solution of 1-*para*-tolylhept-2-yn-1-ol (995 mg, 4.94 mmol, 1.2 equiv) in dichloromethane (35 mL) and the mixture was heated at reflux for 2 h. The solution was cooled to 0°C and then pyridine (1 mL, 12.35 mmol, 3 equiv) and ICl (1.0 M in CH_2Cl_2, 12.4 mL, 12.35 mmol, 3 equiv) were added. The mixture was stirred for 3 h at 0°C. Then, the excess ICl was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield the crude product, which was purified by flash column chromatography on silica gel by using cyclohexane/Et_2O as the eluent (100/0→92/8) to give **7** as a brown solid (1.76 g, 88% yield). M.p. 84°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.91 (t, J=7.6 Hz, 3H; CH_3 *n*Bu), 1.28–1.37 (m, 2H; CH_2 *n*Bu), 1.38–1.49 (m, 2H; CH_2 *n*Bu), 2.07–2.21 (m, 2H; CH_2 *n*Bu), 2.27 (s, 3H; CH_3Ar), 5.64 (s, 1H), 7.18–7.24 (m, 4H; Ar), 7.59 (m, 2H; Ar), 7.71 (tt, J=1.2, 7.6 Hz, 1H; Ar), 7.90 ppm (m, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7, 21.2, 22.1, 25.8, 28.3, 56.9, 74.2, 127.6, 129.1, 129.2, 129.5, 133.6, 134.2, 134.4, 138.8, 156.5 ppm; MS (ESI+): m/z (%): 967 (30) $[2M+H]^+$, 484 (100) $[M+H]^+$, 405 (10), 357 (15), 311 (20), 203 (20); IR (KBr): $\tilde{\nu}$=2957, 1675, 1511, 1446, 1358, 1170, 1087, 1014, 948, 907, 830, 774, 740, 687, 641, 596, 572 cm^{-1}; HRMS (ESI+): m/z calcd for $[C_{20}H_{22}NO_3IS]$: 484.0443; found: 484.0436.

5-Butyl-4-iodo-3-*para*-tolylisoxazole (8): *N*-hydroxybenzenesulfonamide (720 mg, 4.12 mmol, 1 equiv) and $FeCl_3$ (18 mg, 0.103 mmol, 2.5% mol) were added to a solution of 1-*para*-tolylhept-2-yn-1-ol (1.01 g, 4.94 mmol, 1.2 equiv) in dichloromethane (35 mL) and the mixture was heated at reflux for 2 h. The solution was cooled to room temperature, then DMAP (551 mg, 4.54 mmol, 1.1 equiv) was added and the mixture was stirred for 5 h. The solution was then cooled to 0°C, ICl (1.0 M in CH_2Cl_2, 12.4 mL, 12.35 mmol, 3 equiv) was added, and the mixture was stirred for 18 h at 0°C. Then, the mixture was neutralized with aqueous NaOH (3 M). The organic layer was washed with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted with CH_2Cl_2 (2× 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to yield the crude product, which was purified by flash column chromatography on silica gel by using cyclohexane/Et_2O as the eluent (100/0→98/2) to give **8** as a brown solid (1.08 g, 77% yield). M.p. 40°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.98 (t, J=7.2 Hz, 3H; CH_3 *n*Bu), 1.38–1.48 (m, 2H; CH_2 *n*Bu), 1.71–1.79 (m, 2H; CH_2 *n*Bu), 2.42 (s, 3H; CH_3Ar), 2.87 (t, J=7.6 Hz, 2H; CH_2 *n*Bu), 7.29 (d, J=8.4 Hz; 2H; Ar), 7.69 ppm (d, J=8 Hz, 2H; Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 13.7, 21.4, 22.2, 26.8, 29.2, 57.4, 125.8, 128.3, 129.2, 140.0, 162.6, 174.6 ppm; MS (ESI+): m/z (%): 983 (10) $[2M+H]^+$, 342 (100) $[M+H]^+$, 301 (18), 255 (7), 216 (20); IR (neat): $\tilde{\nu}$=3025, 2957, 2929, 2871, 1582, 1567, 1457, 1415, 1380, 1184, 1133, 1106, 1032, 956, 933, 903, 820, 723, 610 cm^{-1}; HRMS (ESI+): m/z calcd for $[C_{14}H_{17}NOI]$: 342.0355; found: 342.0343.

Acknowledgements

We are grateful to the CNRS for financial support (ATIPE jeune équipe), the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette) and the MESR for PhD grants (O.D., E.G., and J.M.C.).

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Received: May 26, 2010
Published online: September 14, 2010

