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Microwave assisted synthesis of dihydropyrrole by AgOAc catalyzed intramolecular cyclization reaction of homopropargyl amine

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Abstract A series of 5-aryl dihydropyrrole was synthesized from the intramolecular cyclization reaction of homopropargyl amine in the presence of AgOAc as catalyst under microwave irradiation reaction conditions. The homopropargyl amine was prepared by the reaction of propargyl bromide with *N*-tosyl aldimine under a sonochemical Barbier-type reaction condition. Further aromatization reaction of 5-aryl dihydropyrrole in KO*t*Bu/DMSO can afford 2-aryl pyrrole under microwave irradiation reaction conditions.

Keywords Homopropargyl amine · Dihydropyrrole · 2-Aryl pyrrole · Sonochemical Barbier-type reaction · Microwave irradiation

Introduction

Pyrroles bearing aryl substituents at the 2-position are often found in a large number of biologically important natural products [1–5], which exhibit interesting biological properties such as the antibacterial [6–9], antifungal [10–12], antitumor [13–15], and used as functional material [16, 17]. Over the years much effort has been directed towards the development of new strategies for 2-arylpyrrole and oligopyrrole synthesis [18–25]. Continuing interest in the development of the synthetic methodology of dihydropyrrole synthesis provides the impetus to initiate a project designed to develop a new and more expedient route to the formation of pyrrole rings. Dihydropyrroles may be employed as important synthetic intermediates for synthesis of pyrroles. Our group reported a sonochemical Barbier-type reaction of propargyl bromide with aldehyde to generate homopropargyl alcohol at room temperature [26] and an intramolecular cyclization of homoallyl alcohol to

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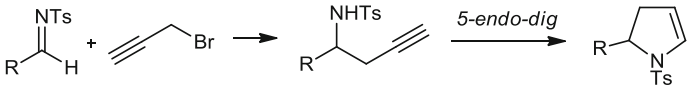


Scheme 1 Synthetic route to homopropargyl amine and dihydropyrrole

afford tetrahydrofuran in the presence of L-proline as a promoter [27]. Our attention was attracted to the formation of homopropargyl amine, which may be achieved by reaction of propargyl bromide with aldimine under our sonochemical Barbier-type reaction conditions, and then this undergoes intramolecular cyclization (5-*endo*-dig) [28] to yield the desired dihydropyrrole (Scheme 1).

Results and discussion

N-Tosylphenyl aldimine was initially chosen as the substrate to be investigated. Treatment of *N*-tosylphenyl aldimine with propargyl bromide under previously developed sonochemical Barbier-type reaction conditions should generate the expected *N*-tosyl homopropargyl amine product. To a reaction mixture of *N*-tosylphenyl aldimine (1.0 eq.) were added zinc powder (5.0 eq.) and 1,2-diiodoethane (1.0 eq.)[1] Propargyl bromide (1.5 eq.) in anhydrous THF (5 mL) was sonicated[2] for 2.5 h and the expected *N*-tosylphenyl homopropargyl amine (78 %) was obtained (Scheme 2). It is worth noting that protection of the alkynyl proton of propargyl bromide was not necessary under this sonochemical Barbier-type reaction conditions [29–36].

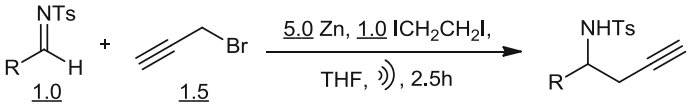
To understand the scope of this sonochemical Barbier-type reaction for synthesis of *N*-tosyl homopropargyl amine, a series of *N*-tosyl aldimines was prepared and investigated, and the results are shown in Table 1.

As shown in Table 1, reactions using aliphatic aldimines (entry 1), electron-poor (entry 3–4) or electron-rich (entries 5, 6) aromatic aldimines, or heteroaromatic aldimines (entries 8, 9) gave the desired *N*-tosyl homopropargyl amines in reasonable to good yields. *N*-tosyl aldimines with highly electron-withdrawing nitro-substituent (entry 4) did not undergo the additional reactions under this sonochemical Barbier-type reaction.

N-Tosylhomopropargyl amines were successfully prepared by the sonochemical Barbier-type reaction conditions. Therefore, the intramolecular cyclization reaction of homopropargyl amine for generating the desired dihydropyrrole was further investigated [37]. *N*-Tosylphenyl homopropargyl amine (Table 1, entry 2) was chosen as the investigated substrate for the intramolecular cyclization reaction (5-*endo*-dig).

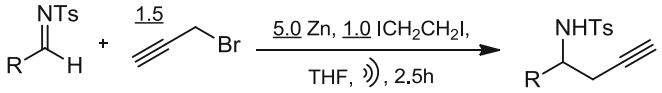
[1] The addition of 1,2-diiodomoethane was used for the activation of metal, and it reacted with Zn powder in situ to generate Lewis acid ZnI_2 and ethene.

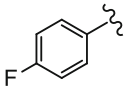
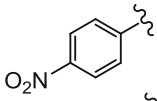
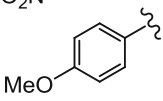
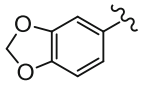
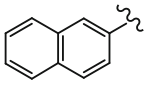
[2] The ultrasonic cleaning bath (Elma-T490DH, 50 kHz) should be filled with water containing some 3–5 % detergent. In our laboratory, we used Decon 90, which permits much more even cavitation in bath water.



Scheme 2 Synthesis of homopropargyl amine by sonochemical Barbier-type reaction

Table 1 Synthesis of homopropargyl amines



Entry	R	Yield[a]
1		57 %
2		78 %
3		83 %
4		S.M.[b]
5		70 %
6		80 %
7		80 %
8		72 %
9		76 %

[a] The yields were determined after chromatographic purification

[b] No reaction and recovery of starting material

After introducing 0.1 eqivalent of AgOAc to *N*-tosylphenyl homopropargyl amine in acetone, the reaction mixture was stirred at 56 °C for 3 days to produce a 35 % yield of dihydropyrrole. In order to shorten the reaction time, the intramolecular cyclization reaction was tested by using a different energy source

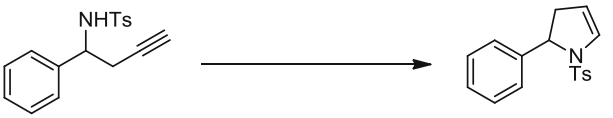
such as microwaves [38–40]. The reaction mixture of AgOAc and *N*-tosylphenyl homopropargyl amine in acetone was irradiated by microwaves at 50 °C ,and the improvment of the dihydropyrrole yield to 54 % was observed after 15 min-irradiation (Scheme 3). It is worth noting that using acetonitrile as solvent instead of acetone dramatically improved the yield from 54 to 76 % under the microwave reaction conditions. Introducing 0.05 equivalent of AgOAc catalyst to homopropargyl amine afforded the same formation yield of dihydropyrrole as provided by using 0.1 equivalent of AgOAc. Other Ag(I)-catalysts were also investigated, and it is interesting to note that generation of dihydropyrrole was not obtained when AgOTf and AgF were used as catalysts, respectively.

To understand the scope of this AgOAc catalyzed intramolecular cyclization of homopropargyl amine, a series of homopropargyl amines was investigated under microwave irradiation conditions and the results are shown in Table 2. As shown in Table 2, all homopropargyl amines were transformed to their corresponding 5-substituted dihydropyrroles with moderate to high yields. Both alkyl- and aryl homopropargyl amines can undergo this Ag(I)-catalyzed intramolecular cyclization reaction and gave the desired products.

The synthesis of 5-aryl dihydropyrroles was exploited and further aromatized to their corresponding pyrroles, which are valuable precursors in the synthesis of biologically active compounds and materials. Therefore, the ability to access the aromatization reaction to generate aryl pyrrole was investigated. Conventional aromatizating agents such as P-Chloranil (tetrachloro-1,4-benzoquinone) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) failed to generate the expected 2-aryl pyrrole. Many products were obtained, and the structures of these formed compounds were not identified. Thus, other reaction conditions were examined to investigate their affects on the oxidation of 5-aryl dihydropyrrole to 2-aryl pyrrrole. We Introduced 5.0 equivalents of potasium *tert*-butyloxide to 5-phenyl dihydropyrrole in DMSO, and the reaction mixture was stirred at room temperature for 4 h. Only the recovered starting material was observed. The reaction mixture of *t*-BuOK and 5-phenyl dihydropyrrole in DMSO was irradiated by microwaves at 50 °C for 5 min, and the expected product 2-phenyl pyrrole was obtained with 47 % yield (Scheme 4). It should be noted that the *N*-tosyl group of pyrrole was not resistant under this basic reaction condition and was hydrolyzed to its corresponding 1H-pyrrole.

Thus, a series of 5-aryl dihydropyrroles was investigated under the microwave irradiation conditions, and the results are shown in Table 3. As shown in Table 3, all 5-aryl dihydropyrroles were transformed to their corresponding 2-aryl pyrroles with reasonable yields.

In conclusion, a new method for preparation of homopropargyl amine was developed by the reaction of propargyl bromide with aldimine under sonochemical Barbier-type reaction conditions. 5-Aryl dihydropyrrole was synthesized from the AgOAc catalyzed intramolecular cyclization reaction of homopropargyl amine under microwave irradiation reaction conditions. Further aromatization reaction of 5-aryl dihydropyrrole in KO*t*Bu/DMSO affords 2-aryl pyrrole under microwave irradiation reaction conditions.



* 10% AgOAc, Acetone, 56 °C, 3 days	35%
* 10% AgOAc, Acetone, μω 50 °C, 15 min	54%
* 10% AgOAc, CH_3CN, μω 80 °C, 15 min	76%
* 5% AgOAc, CH_3CN, μω 80 °C, 15 min	74%
* 5% AgOTf, CH_3CN, μω 80 °C, 15 min	N.R. (S.M.)
* 5% AgF, CH_3CN, μω 80 °C, 15 min	N.R. (S.M.)

Scheme 3 Optimization of cyclization reaction of homopropargyl amine

Experimental section

All reagents were purchased from Aldrich, Merck and Riedel–deHaen, and all were used directly without further purification. The microwave irradiation reaction was carried out in a CEM Discover microwave reactor. The ^{1}H-NMR (proton nuclear magnetic resonance) spectra were recorded at 300 MHz (Bruker-AC300P) with deuteriochloroform ($CDCl_3$, Aldrich 99.8 atom% D) as the solvent and the internal standard. The ^{13}C-NMR (carbon nuclear magnetic resonance) spectra were recorded at 75.5 MHz (Bruker-AC300P) with $CDCl_3$ as the solvent and the internal standard. Column chromatography was performed using silica gel (Merck 230–400 mesh) and ethyl acetate/hexane mixture as the eluent.

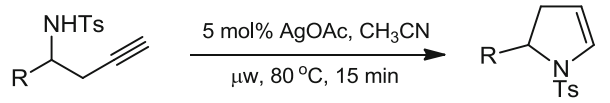
A representative procedure for synthesis of homopropargyl amines

A solution of *N*-tosylphenyl aldimine (1.0 mmol) and propargyl bromide (1.5 mmol) in anhydrous THF (5 mL) was added dropwise to a reaction mixture of zinc (5.0 mmol) and 1,2-diiodoethane (see footnote 1) (1.0 mmol) in anhydrous THF (25 mL) under sonication in a commercial ultrasonic cleaning bath (see footnote 2) (Elma-T490DH, 50 *k*Hz) for 2.5 h at around 43 °C. After sonication, an aqueous 2M HCl (10 mL) was added, and the filtrate was extracted with ether (30 mL × 3). The combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, filtered, and then the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with ethyl acetate/hexane as eluent.

A representative procedure for synthesis of 5-substituted dihydropyrroles

A reaction mixture of homopropargyl amine (1.0 mmol), AgOAc (0.05 mmol) in CH_3CN (4 mL) was introduced in a pressure tube with a threaded Teflon cap, and the reaction mixture was microwave-irradiated for 15 min at 100 W, 100 psi, and

Table 2 Synthesis of *N*-tosyl dihydropyrroles



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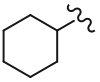
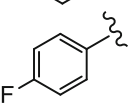
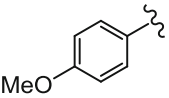
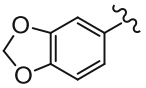
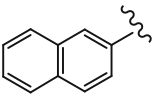
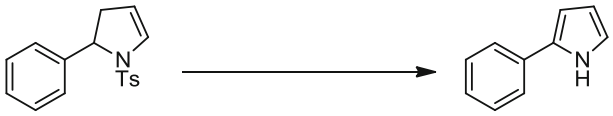
1		60 %
2		75 %
3		85 %
4		74 %
5		78 %
6		91 %
7		87 %
8		81 %

[a] The yields were determined after chromatographic purification

80 °C reaction condition. The reaction mixture was cooled to room temperature, and the resulting product was passed through a short Celite column to remove metals. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane as eluent.

A representative procedure for synthesis of 2-substituted pyrroles

A reaction mixture of dihydropyrrole (1.0 mmol) and KO*t*Bu (5.0 mmol) in DMSO (Dimethyl sulfoxide, 4 mL) was introduced in a pressure tube with a threaded Teflon cap, and the reaction mixture was microwave-irradiated for 5 min at 100 W, 100 psi, and 50 °C reaction conditions. The reaction mixture was cooled to room temperature, and ether (30 mL) was added. The resulting solution was passed through a short Celite column to remove metals. The combined organic layer was



* 5.0 *t*-BuOK, DMSO, rt, 4 h	N.R. (S.M)
* 5.0 *t*-BuOK, DMSO, μω 50 °C, 5 min	47%
* 0.75 P-Chloranil, CH_3CN, μω 80 °C, 5 min	Unknown
* 0.75 DDQ, CH_3CN, μω 80 °C, 5 min	Unknown

Scheme 4 Optimization of aromitization of dihydropyrrole

washed with water (20 mL × 3), brine (20 mL), dried with $MgSO_4$, filtered, and then the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane as eluent.

N-(1-cyclohexylbut-3-ynyl)-4-methylbenzenesulfonamide (Table 1, Entry 1)

^{1}H-NMR: δ0.91 (m, 2H), 1.07 (m, 3H), 1.53 (m, 6H), 1.92 (m, 1H), 2.17 (m, 1H), 2.27 (m, 1H), 2.41 (s, 3H), 3.08 (m, 1H), 4.71 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H). ^{13}C-NMR: δ21.3, 22.0, 25.6, 28.0, 29.2, 39.8, 56.3, 71.0, 79.5, 126.8, 129.3, 137.9, 143.0.

4-methyl-N-(1-phenylbut-3-ynyl)benzenesulfonamide (Table 1, Entry 2)

^{1}H-NMR: δ1.97 (t, J = 2.6 Hz, 1H), 2.38 (s, 3H), 2.64 (m, 2H), 4.50 (q, 1H), 5.02 (d, J = 6.8 Hz, 1H), 7.14–7.23 (m, 7H), 7.62 (d, J = 8.2 Hz, 2H). ^{13}C-NMR: δ21.3, 27.1, 55.8, 71.8, 79.1, 126.5, 126.9, 127.6, 128.2, 129.2, 137.1, 139.0, 143.1.

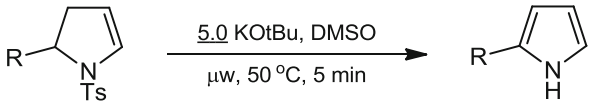
N-(1-(4-fluorophenyl)but-3-ynyl)-4-methylbenzenesulfonamide (Table 1, Entry 3)

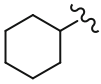
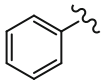
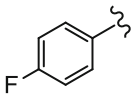
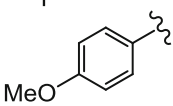
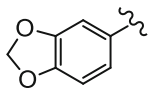
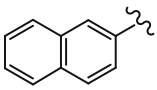
^{1}H-NMR: δ1.99 (t, J = 2.5 Hz 1H), 2.39 (s, 3H), 2.58–2.61 (m, 2H), 4.45 (q, 1H), 5.17 (s, 1H), 6.86–6.92 (m, 2H), 7.12 (m, 2H), 7.17 (m, 2H), 7.58 (d, J = 8.25 Hz, 2H). ^{13}C-NMR: δ21.4, 27.2, 55.1, 72.2, 78.8, 115.0, 127.0, 128.2, 129.4, 134.9, 137.0, 143.4, 160.9, 163.3.

N-(1-(4-methoxyphenyl)but-3-ynyl)-4-methylbenzenesulfonamide (Table 1, Entry 5)

^{1}H-NMR: δ1.98 (t, 1H), 2.39 (s, 3H), 2.62 (m, 2H), 3.76 (s, 3H), 4.44 (m, 1H), 5.02 (d, J = 6.82 Hz, 1H), 6.72 (d, J = 6.7 Hz, 2H), 7.07 (d, J = 6.7 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H). ^{13}C-NMR: δ21.4, 27.5, 29.3, 55.5, 55.7, 70.8, 71.8, 79.5, 114.1, 127.4, 128.2, 129.4, 131.4, 137.4, 143.1, 159.1.

Table 3 Synthesis of 2-substituted pyrroles



Entry	R	Yield[a]
1		59 %
2		42 %
3		62 %
4		85 %
5		54 %
6		23 %
7		50 %
8		64 %

[a] The yields were determined after chromatographic purification

N-(1-(benzo[d] [1,3] dioxol-5-yl)but-3-ynyl)-4-methylbenzenesulfonamide (Table 1, Entry 6)

^{1}H-NMR: δ2.00 (s, 1H), 2.39 (s, 3H), 2.57 (m, 2H), 4.36 (m, 1H), 5.15 (m, 1H), 5.88 (d, $J = 5.6$ Hz 1H), 6.59 (m, 3H), 7.18 (d, $J = 8.1$ Hz, 2H), 7.59 (d, $J = 8.1$ Hz, 2H). ^{13}C-NMR: δ21.4, 27.2, 55.6, 72.0, 79.1, 101.0, 106.9, 107.8, 120.2, 127.0, 129.3, 133.0, 137.1, 143.2, 147.0, 147.4.

4-methyl-N-(1-(naphthalen-2-yl)but-3-ynyl)benzenesulfonamide (Table 1, Entry 7)

^{1}H-NMR: δ1.99 (m, 1H), 2.33 (s, 3H), 2.79 (m, 2H), 5.27 (m, 2H), 7.06 (d, $J = 7.9$ Hz, 2H), 7.32 (d, $J = 7.9$ Hz, 1H), 7.42 (m, 3H), 7.44 (m, 2H), 7.55 (m,

1H), 7.57(m, 1H). ^{13}C-NMR: δ21.5, 26.8, 56.0, 72.6, 79.2, 124.5, 125.8, 126.4, 126.6, 127.3, 127.5, 128.6, 129.1, 129.4, 130.2, 133.9, 134.5, 137.1, 143.4.

N-(1-(furan-2-yl)but-3-ynyl)-4-methylbenzenesulfonamide (Table 1, Entry 8)

^{1}H-NMR: δ1.98 (s, 1H), 2.39 (s, 3H), 2.65 (m, 2H), 4.58 (m, 1H), 5.18 (d, $J = 8.40$ Hz, 1H), 6.12 (d, $J = 3.3$ Hz 1H), 6.19 (m, 1H), 7.23 (m, 1H), 7.29 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H). ^{13}C-NMR: δ21.4, 25.0, 49.9, 71.8, 78.7, 107.6, 110.2, 127.0, 129.5, 137.3, 142.2, 143.3, 151.4.

4-methyl-N-(1-(thiophen-2-yl)but-3-ynyl)benzenesulfonamide (Table 1, Entry 9)

^{1}H-NMR: δ2.02 (t, $J = 2.6$ Hz, 1H), 2.41 (s, 3H), 2.72 (dd, $J = 2.6$, 2.8 Hz, 2H), 4.76 (m, 1H), 5.12 (d, $J = 8.1$ Hz, 1H), 6.83 (m, 2H), 7.14 (m, 1H), 7.23 (d, $J = 8.2$ Hz, 1H), 7.68 (d, $J = 8.2$ Hz, 1H). ^{13}C-NMR: δ21.5, 27.6, 51.6, 72.5, 78.7, 125.2, 126.6, 127.1, 129.5, 137.2, 142.8, 143.5.

2-cyclohexyl-1-tosyl-2,3-dihydro-1H-pyrrole (Table 2, Entry 1)

^{1}H-NMR: δ1.08 (m, 3H), 1.16 (m, 5H), 1.73 (m, 3H), 2.14 (m, 2H), 2.42 (s, 3H), 3.58(m, 1H), 5.06 (m, 1H), 6.28(m, 1H), 7.27 (d, $J = 8.3$ Hz, 2H), 7.64 (d, $J = 8.3$ Hz, 2H). ^{13}C-NMR: δ21.3, 22.0, 25.8, 29.2, 39.8, 56.3, 76.0, 79.5, 127.1, 129.1, 137.9, 143.0.

2-phenyl-1-tosyl-2,3-dihydro-1H-pyrrole (Table 2, Entry 2)

^{1}H-NMR: δ2.42 (m, 4H), 2.86 (m, 1H), 4.69 (m, 1H), 5.09 (m, 1H), 6.51 (m, 1H), 7.23 (m, 1H), 7.27 (m, 7H), 7.53 (d, $J = 8.2$ Hz, 2H). ^{13}C-NMR: δ21.6, 40.8, 63.0, 109.9, 126.6, 127.7, 127.9, 129.6, 129.8, 131.0, 134.2, 143.7, 147.1.

2-(4-fluorophenyl)-1-tosyl-2,3-dihydro-1H-pyrrole (Table 2, Entry 3)

^{1}H-NMR: δ2.35 (m, 4H), 2.83 (m, 1H), 2.75 (m, 1H), 4.67 (m, 1H), 5.10 (m, 1H), 6.51 (m, 1H), 6.95 (m, 2H), 7.27 (m, 4H), 7.59 (d, $J = 8.2$ Hz, 2H). ^{13}C-NMR: δ21.4, 40.5, 62.2, 110.0, 127.0, 127.4, 127.8, 127.9, 129.5, 129.6, 130.6, 133.6, 138.4, 143.8, 160.8, 163.2.

2-benzo [1,3] dioxol-1-tosyl-2,3-dihydro-1H-pyrrole (Table 2, Entry 4)

^{1}H-NMR: δ2.42 (s, 3H), 2.46 (m, 1H), 2.87 (m, 1H), 3.78 (s, 3H), 4.64 (m, 1H), 5.09 (m, 1H), 6.49 (m, 1H), 6.81 (d, $J = 6.6$ Hz, 2H), 7.22 (m, 4H), 7.59 (d, $J = 8.2$ Hz, 2H). ^{13}C-NMR: δ21.6, 32.2, 32.8, 34.6, 55.3, 62.4, 64.2, 64.8, 84.9, 85.5, 89.8, 113.9, 127.3, 127.8, 128.1, 129.8, 133.8, 134.9, 136.0, 143.5, 158.9.

2-(4-methoxyphenyl)-1-tosyl-2,3-dihydro-1H-pyrrole (Table 2, Entry 5)

^{1}H-NMR: δ2.42(s, 3H), 2.50(m, 1H), 2.91(m, 1H), 4.72(m, 1H), 5.11(m, 1H), 6.52(m, 1H), 7.29(m, 6H), 7.61(d, $J = 8.00$ Hz, 2H). ^{13}C-NMR: δ21.7, 40.8, 63.1, 110.2, 126.4, 126.6, 127.6, 127.7, 128.7, 129.7, 129.8, 130.9, 142.8, 143.8.

2-(naphthalen-2-yl)-1-tosyl-2,3-dihydro-1H-pyrrole (Table 2, Entry 6)

^{1}H-NMR: δ2.42 (s, 3H), 2.43 (m, 1H), 3.06 (m, 1H), 5.15 (s, 3H), 5.35 (m, 1H), 6.65 (m, 1H), 7.27 (m, 2H), 7.42 (m, 3H), 7.54 (m, 3H), 7.75 (m, 2H), 7.85 (m, 1H). ^{13}C-NMR: δ21.5, 29.6, 40.2, 110.4, 122.9, 124.2, 125.3, 125.4, 125.9, 127.6, 128.0, 129.0, 129.5, 129.8, 130.9, 133.5, 134.0, 137.4, 143.7.

N-(1-(furan-2-yl)but-3-ynyl)-4-methylbenzenesulfonamide (Table 2, Entry 7)

^{1}H-NMR: δ2.41 (s, 3H), 2.61 (m, 1H), 2.83 (m, 1H), 5.05 (m, 1H), 5.15 (m, 1H), 6.43 (m, 1H), 6.89 (m, 1H), 7.17 (m, 1H), 7.26 (d, $J = 8.2$ Hz, 2H), 7.60 (d, $J = 8.2$ Hz, 2H). ^{13}C-NMR: δ21.4, 36.2, 56.4, 70.1, 74.7, 107.4, 110.3, 110.5, 127.0, 128.7, 129.5, 133.6, 142.3, 153.2

2-(thiophen-2-yl)-1-tosyl-2,3-dihydro-1H-pyrrole (Table 2, Entry 8)

^{1}H-NMR: δ2.41 (s, 3H), 2.61 (m, 1H), 2.83 (m, 1H), 5.05 (m, 1H), 5.15 (m, 1H), 6.43 (m, 1H), 6.89 (m, 1H), 7.17 (m, 1H), 7.26 (d, $J = 8.2$ Hz, 2H), 7.60 (d, $J = 8.2$ Hz, 2H). ^{13}C-NMR: δ21.6, 32.8, 34.7, 60.5, 85.6, 89.9, 124.9, 125.4, 126.8, 127.3, 127.6, 130.0, 135.9, 143.7, 147.3.

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