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PII: S0040-4020(17)30162-X

DOI: 10.1016/j.tet.2017.02.030

Reference: TET 28471

To appear in: *Tetrahedron*

Received Date: 6 January 2017

Revised Date: 13 February 2017

Accepted Date: 14 February 2017

Please cite this article as: Tao R, Yin Y, Duan Y, Sun Y, Sun Y, Cheng F, Pan J, Lu C, Wang Y, Fe(OTf)$_3$-catalyzed tandem Meyer-Schuster rearrangement/intermolecular hydroamination of 3-aryl propargyl alcohols for the synthesis of acyclic β-Aminoketones, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.02.030.

Graphical Abstract

$Fe(OTf)_3$-Catalyzed Tandem Meyer-Schuster Rearrangement/Intermolecular Hydroamination of 3-Aryl Propargyl Alcohols for the Synthesis of Acyclic β-Aminoketones

Ruiheng Tao[a], Yan Yin[a, b,]*, Yongbin Duan[a], Yuxing Sun[a], Yue Sun[a], Fengkai Cheng[a], Jinpeng Pan[a], Cheng Lu[a], and Yuan Wang[a]

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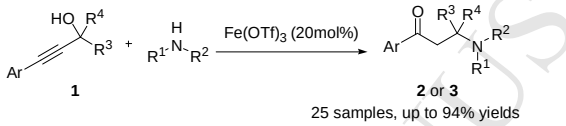

25 samples, up to 94% yields

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Fe(OTf)$_3$-Catalyzed Tandem Meyer-Schuster Rearrangement/Intermolecular Hydroamination of 3-Aryl Propargyl Alcohols for the Synthesis of Acyclic β-Aminoketones

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Meyer-Schuster rearrangement
intermolecular hydroamination
propargyl alcohols
Fe(OTf)$_3$
β-aminoketones

ABSTRACT

Fe(OTf)$_3$-catalyzed synthesis of acyclic β-aminoketones from 3-aryl propargyl alcohols and nitrogen nucleophiles were investigated. Results showed that propargyl alcohols without bulky groups α to the hydroxyl group underwent the transformation smoothly. Sulphonamides exhibited the higher reactivity than amides as the nitrogen nucleophiles and the transformation of acyclic β-aminoketones were finished in shorter reaction time and higher yields. Finally, racemic fluoxetine was efficiently accessed with the present reaction as the first step. This novel synthesis of acyclic β-aminoketones probable proceeded a Fe(OTf)$_3$-catalyzed Meyer-Schuster rearrangement of 3-aryl propargyl alcohols, followed by a intermolecular hydroamination between nitrogen nucleophiles and α, β-unsaturated ketones.

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1. Introduction

β-Aminoketone is an important building block in organic synthesis, which can easily be converted to α, β-unsaturated ketone, 1, 3-amino alcohol and other functionalized ketone,[1]and β-amino carbonyl compounds exhibit numerous biological activities including anti-inflammatory, anticancer, anti-tuberculosis, antibacterial, analgesic and antitussive activities.[2] As a result, various methods for the preparation of β-aminoketone have been developed.[3] Mannich-type reaction might be the most popular methodology for the one-pot construction of β-aminoketone with substitution at nitrogen which has been studied by organic chemists for decades.[4] Copper(II) acetate catalyzed ring-opening cross-coupling of cyclopropanols with sulfonylazide is an alternative strategy.[5]Aminobromination of α, β-unsaturated ketones with sulfonamide and NBS afforded the corresponding halo acyclic β-aminoketones in excellent yields and selectivities.[6] Morken reported a one-pot synthesis of β-amidoketones from allenes in good yields and high enantioselectivities.[7] Convenient access to heterocycle-containing β-aminoketones through a direct *N*-methylation reaction using DMSO as the one-carbon bridge was exlporated by Sun.[8] Recently, Shi reported a direct oxidation of the aliphatic C-H bonds of primary amines and amino acids as well as dipeptides to the corresponding oxo products.[9] Although much attention has been paid to construct theβ-aminoketone unit, development of new synthetic methodology for this privileged structure is still an important and challenging task for the chemistry community.

Recently, Yanada demonstrated that electron-rich primary propargyl alcohols undergo $Bi(OTf)_3$-catalyzed Meyer-Schuster rearrangement and successive 1,4-addition of alcohol to give β-alkoxyketones, they also extend this tandem reaction to a one-pot dihydroquinolone synthesis (Figure 1, Scheme A).[10] Our group developed a superacid-catalyzed intramolecular cyclization of o-aniliopropargy alcohols to the synthesis of 2,3-dihydro-4(1H)-quinolone (Figure 1, Scheme B).[11] The transformation in both Scheme A and Scheme B was accessed through rearrangement of propargyl alcohols to the corresponding α, β-unsaturated aldehydes, and the intramolecular hydroamination of nitrogen to olefins. In this work, we would like to investigate the acid-catalyzed reaction between 3-aryl propargyl alcohols and nitrogen nucleophiles for the synthesis of acyclic β-aminoketones (Figure 1, Scheme C).

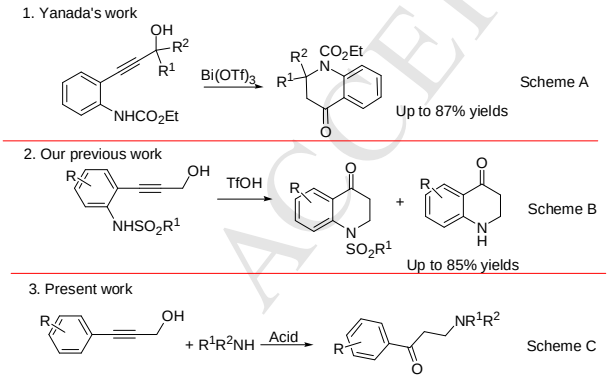
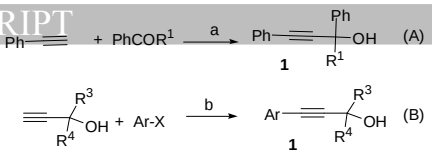


Figure 1 Tandem Meyer-Schuster rearrangement/hydroamination

2. Results and discussion

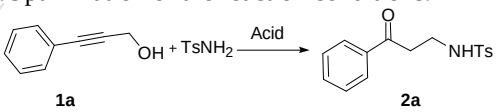
2-Substituted 1,3-diphenyl-prop-2-yn-1-ols were accessed through the nucleophilic addition of phenylacetylen to phenyl carbonyl compounds (Scheme 1, A).[12] Other 3-aryl substituted propargyl alcohols were synthesized through Pd^{2+}-catalyzed Sonogashina coupling reaction of Ar-X and commercial available prop-2-yn-1-ols (Scheme 1, B).[13]



Scheme 1.Synthesis of **1**. Reagents and conditions: (a) n-BuLi, THF, -78^{O}C-rt, (b) $PdCl_2(PPh_3)_2$, CuI, Et_3N, 80^{O}C.

For the efficient access to acyclic β-aminoketones, the reaction conditions between 3-phenyl-prop-2-yn-1-ol **1a** and $TsNH_2$ were firstly optimized (Table 1). Catalyzed with 20 mol% of acids including TfOH, AgOTf, $Cu(OTf)_2$, or $Sc(OTf)_3$, 4-methyl-*N*-(3-oxo-3-phenyl-propyl)-benzenesulfonamide **2a** were separated in moderate yields (entries 1-4). Treating with 20 mol% of $Bi(OTf)_3$ or $Fe(OTf)_3$, **2a** were obtained in 92% and 94% yields after 16 hours, respectively (entries 5-6). While 20 mol% of $FeCl_3$ was added, unanticipated *N*-(3-chloro-3-phenyl-allyl)-4-methyl-benzenesulfonamide was separated (entry 7). Then dioxane, DCE, benzene, THF and toluene were compared as solvents, dioxane exhibited to be the best solvent among them and unconsumed **1a** was recovered (entries 6, and 8-11). Catalyst loading studies showed that 10 mol% of $Fe(OTf)_3$ cause very low yield of **2a** and 30 mol% of $Fe(OTf)_3$ had the similar yield and reaction time as 20 mol% of $Fe(OTf)_3$ (entries 12 and 13 vs. 6). Out of our expectation, dimeric diketone was separated while decreasing $TsNH_2$ to 1 equivalence (entries14), and increasing $TsNH_2$ to 3 equivalence had no effect on the yield compared with 2 equivalence of $TsNH_2$ (entries 15 vs. 6). So the optimized reaction conditions for this transformation were 20 mol% of $Fe(OTf)_3$ as the catalyst, 2 equivalence of nitrogen nucleophile, and dioxane as solvent.

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Temp. (^{O}C)	Catalyst loading (mol%)	$TsNH_2$ (equiv.)	Time (h)	**2a** (%)[b]
1	TfOH	α, α, α,-Trifluorotoluene	110	20	2	6	50
2	AgOTf	Dioxane	110	20	2	31	62
3	$Cu(OTf)_2$	Dioxane	110	20	2	20	59
4	$Sc(OTf)_3$	Dioxane	110	20	2	33	51
5	$Bi(OTf)_3$	Dioxane	110	20	2	16	92
6	$Fe(OTf)_3$	Dioxane	110	20	2	16	94
7	$FeCl_3$	Dioxane	110	20	2	11	50
8	$Fe(OTf)_3$	THF	70	20	2	48	9[c]
9	$Fe(OTf)_3$	DCE	90	20	2	48	39[c]
10	$Fe(OTf)_3$	Benzene	90	20	2	18	34[c]
11	$Fe(OTf)_3$	Toluene	110	20	2	13	42[c]
12	$Fe(OTf)_3$	Dioxane	110	10	2	48	42[c]
13	$Fe(OTf)_3$	Dioxane	110	30	2	14	94
14	$Fe(OTf)_3$	Dioxane	110	20	1	17	85

15	$Fe(OTf)_3$	Dioxane	110	20	3	14	94

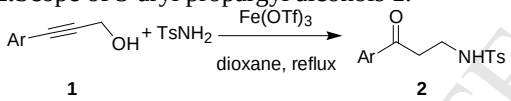
[a] Reaction conditions: **1a** (0.2 mmol), solvent (1 mL).

[b] Isolated yield after flash chromatography.

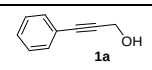
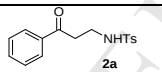
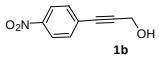
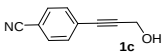
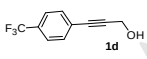
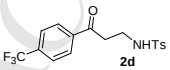
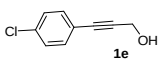
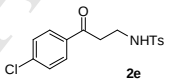
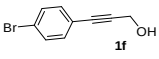
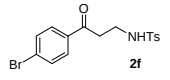
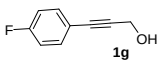
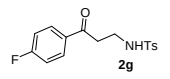
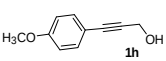
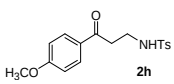
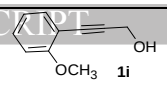
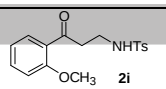
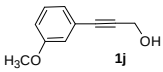
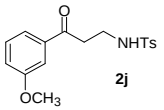
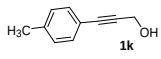
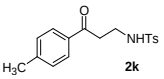
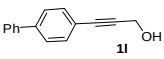
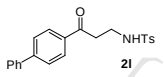
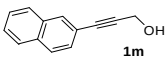
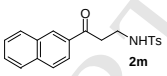
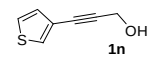
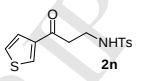
[c] The unconsumed **1a** was recovered.

In Yanada's investigation, only 3-phenyl-prop-2-yn-1-ol derivatives with electronic donating group on the phenyl ring underwent $Bi(OTf)_3$-catalyzed tandem Meyer-Schuster rearrangement and 1, 4-addition to the resulting vinyl ketone.[10] We then explored the scope of 3-aryl propargyl alcohols under the optimized reaction conditions (Table 2). Propargyl alcohols (**1a-1p**) with different Ar groups on the triple bond were prepared according to Scheme 1, which may alter the electron density of the triple bond. The difference of substitutions in the phenyl ring had obvious effects on the reaction times and yields (entries 1-11). There were no transformation for 3-aryl propargyl alcohols with very electronic withdrawing groups (NO_2 and CN), and the starting materials (**1b** and **1c**) were recovered (entries 2 and 3). 3-Aryl propargyl alcohols with weaker electronic withdrawing group (4-CF_3 and 4-Cl) underwent the transformation slowly and low yields were obtained (entries 4 and 5). To our surprise **2f** was formed in 80% yield after 21 hours from **1f** with 4-Br-substituion and 85% yield for **2g** after 10 hours from **1g** with 4-F-substituion (entries 6 and 7). The similar results as Yanada's investigation were obtained, electronic donating substitutions, such as 4-OCH_3, 2-OCH_3, 3-OCH_3, and 4-Ph, were benefit for this reaction (93% yield for **1h** with 4-OCH_3 after 3 hours, 91% yield for **1i** with 2-OCH_3 after 12 hours, 85% yield for **1j** with 3-OCH_3 after 29 hours, 89% yield for **1k** with 4-CH_3 after 15 hours, and 92% yield for **1l** with 4-Ph after 9 hours, entries 8-12). Expanding phenyl ring to naphthalenyl and thiophenyl rings, products **2o** and **2p** were obtained in high yields (entries 13 and 14). However, replacement of aromatic ring to alkyl group including CH_3 and CH_2CH_3 led to no reaction.

Table 2. Scope of 3-aryl propargyl alcohols **1**.[a]



1 **2**

Entry	Alcohol	Product	Time(h)	Yield (%)[b]
1	 **1a**	 **2a**	16	94
2	 **1b**	-	72	NR[c]
3	 **1c**	-	72	NR[c]
4	 **1d**	 **2d**	72	10[c]
5	 **1e**	 **2e**	72	47
6	 **1f**	 **2f**	21	80
7	 **1g**	 **2g**	10	85
8	 **1h**	 **2h**	3	93
9	 **1i**	 **2i**	12	91
10	 **1j**	 **2j**	21	85
11	 **1k**	 **2k**	15	89
12	 **1l**	 **2l**	9	92
13	 **1m**	 **2m**	10	84
14	 **1n**	 **2n**	17	91

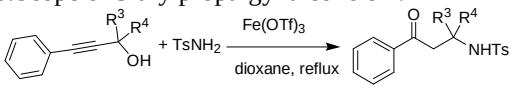
[a] Reaction conditions: Alcohol (0.2 mmol), $TsNH_2$ (0.4 mmol), $Fe(OTf)_3$ (0.04 mmol), dioxane (1 mL), 110^{O}C.

[b] Isolated yield after flash chromatography.

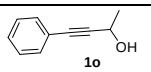
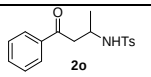
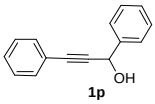
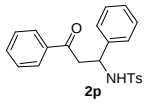
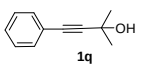
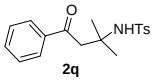
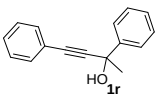
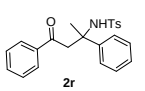
[c] Unconsumed **1** was recovered.

We then turned our attention to secondary and tertiary alcohols (Table 3). The reactions of the more sterically hindered alcohols resulted in hardly proceeding to this tandem reaction and almost could not obtain the corresponding β-aminoketones. Secondary alcohols (**1o** and **1p**) transferred to β-aminoketones in 30% and 10% yields after 6 hours, respectively, and by-products were separated (entries 1 and 2). Only a complex mixture was detected and no β-aminoketones were separated with tertiary alcohols (**1q** and **1r**) as the starting materials (entries 3 and 4).

Table 3. Scope of 3-arylpropargyl alcohols **1**.[a]



1 **2**

Entry	Alcohol	Product	Time(h)	Yield(%)[b]
1	 **1o**	 **2o**	6	30
2	 **1p**	 **2p**	6	10
3	 **1q**	 **2q**	6	0
4	 **1r**	 **2r**	6	0

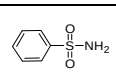
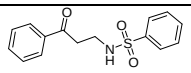
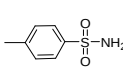
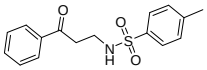
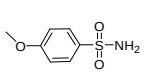
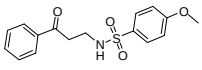
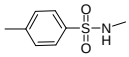
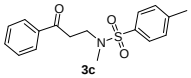
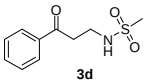
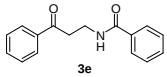
[a] Reaction conditions: Alcohol (0.2 mmol), $TsNH_2$ (0.4 mmol), $Fe(OTf)_3$ (0.04 mmol), dioxane (1mL), 110^{O}C.

[b] Isolated yield after flash chromatography.

Subsequently, we examined the scope of nitrogen nucleophiles with **1a** as the propargyl alcohol, and the results were summarized in **Table 4**. Sulfonamides were well tolerated and afforded the corresponding β-aminoketones in high isolated yields (entries 1-5). Increasing the nucleophilicity of benzenesulfonamides resulted in higher rate and yield of the reaction (entries 1-3). Secondary benzenesulfonamide could be employed for this reaction, and $TsNHCH_3$ gave **3c** in 81% yield (entry 4). Benzamide showed low reactivity and only 8% yields of **3e** were obtained after 16 hours (entry 6). Trifluoroacetamide

and aniline could not give the corresponding β-aminoketones due to the low nucleophilicity (entries 7 and 8).

Table 4. Scope of the nitrogen nucleophiles.[a]

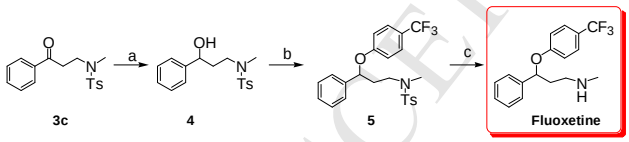
Entry	Nucleophile	Product	Time(h)	Yield(%)[b]
1		 **3a**	22	91
2		 **2a**	16	94
3		 **3b**	14	95
4		 **3c**	18	92
5		 **3d**	19	81
6		 **3e**	16	8[c]
7		-	16	NR[c]
8		-	16	NR[c]

[a] Reaction conditions: Alcohol (0.2 mmol), Nucleophile (0.4 mmol), $Fe(OTf)_3$ (0.04 mmol), dioxane (1mL), 110^{O}C.

[b] Isolated yield after flash chromatography.

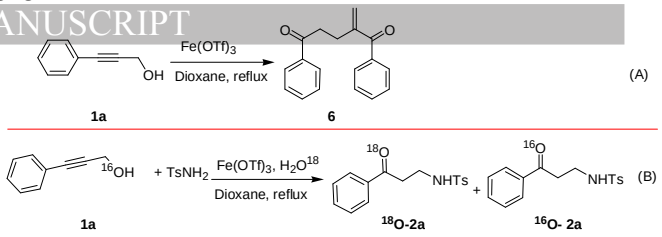
[c] Unconsumed **1a** was recovered.

Fluoxetine, marketed under the trade name Prozac, offers the treatment of anxiety, alcoholism, chronic pain, headache, obsessive disorders, sleepdisorders, and bulimia.There have been several reports on the synthesis of racemic fluoxetine and optical fluoxetine.[14]As shown in Figure 2, racemic fluoxetine was successfully accomplished by reduction of compound **3c** with $NaBH_4$ in methanol, etherification with 4-chlorobenzotrifluoride and sodium hydride in dimethylsulfoxide, and subsequent deprotection with Na/Naphthalene. Finally, an easy and novel approach for the total synthesis of racemic fluoxetine were discovered, and the total yield was 59% from **1a** after 4 steps.



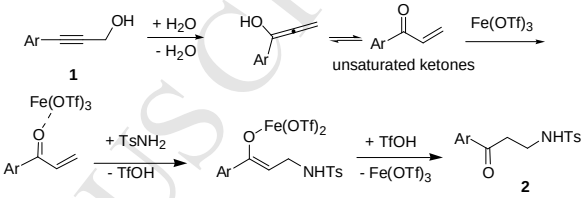
Scheme 2.Synthesis of **racemic Fluoxetine**. Reagents and conditions: (a) $NaBH_4$, MeOH; (b) NaH, 1-chloro-4-trifluoromethyl-benzene, DMSO; (c) Na, naphthalene, glycol dimethyl ether.

Additional experiments shed some light on the reaction mechanism. Treatment of **1a** with stoichiometric amounts of $Fe(OTf)_3$ led to dimeric diketone **6**, which was reported by Yanada previously (Scheme 3, A).[10] Refluxing **1a** with 20 mol% of $Fe(OTf)_3$, 2 equivalences of $TsNH_2$, 1 equivalence of $H_2{}^{18}O$, and dioxane led to both **^{18}O-2a** and **^{16}O-2a** detected by HRMS (Scheme 3, B), which meant that the removal of ^{16}O in **1a** and the addition of ^{18}O in $H_2{}^{18}O$ were took place during the reaction.



Scheme 3. Mechanistic evidences

Based on the knowledge of the transformation of propargyl alcohols into α, β-unsaturatedketones[15] and the mechanistic evidences in Scheme 3, we proposed a possible mechanism of present reaction (Scheme 4). Propargylic alcohols easily lost a H_2O and added a H_2O in the presence of catalytic amounts of $Fe(OTf)_3$. Then keto-enol tautomerism afforded α, β-unsaturated ketones. Coordination of the carbonyl group to $Fe(OTf)_3$ followed by nucleophilic addition of $TsNH_2$ afforded coordinated enol intermediate. Protonation of enol intermediate provided products **2** and regenerated catalyst $Fe(OTf)_3$.



Scheme 4. Plausible mechanism

3. Conclusion

In summary, we developed a $Fe(OTf)_3$-catalyzed tandem Meyer-Schuster rearrangement/1,4-addition of 2-aryl propargyl alcohols with nitrogen nucleophiles to give acyclic β-aminoketones, and this methodology was successfully used in the synthesis of racemic fluoxetine. The $Fe(OTf)_3$ catalyst probably played a dual role in the rearrangement of propargyl alcohols to the corresponding unsaturated ketones and intermolecular hydroamination of nucleophiles to unsaturated ketones. Our studies indicated a low catalyst loading and high yield reaction, making it a potentially attractive method in organic synthesis of acyclic β-aminoketones. More reactions between propargyl alcohols and nucleophiles were underway in our lab and will be published in due course.

4. Experimental section

4.1. General information

Commercially available reagents and anhydrous solvents were used without further purification unless otherwise specified. Thin layer chromatography (TLC) analyses were performed with Huanghai TLC plates. All the products were purified by column chromatography on silica gel with ethyl acetate-hexane in an appropriate ratio as the eluent. ^1H and ^{13}C NMR spetra were recorded at Bruker 500- or 400-MHz instrument with TMS as an internal standard. IR spectra (KBr) were recorded on a FT-IR spectrometer in the range of 400-4000cm^{-1}.The melting points were measure on a SGWX-4 instrument. High-resolution mass spectrographic (HRMS) experiments were performed with Thermo Finnigan Orbitrap mass analyzer.

*4.2. Preparation of **1a-1o** and **1q***

To a mixture of aryl halide (1 mmol) in Et_3N (4 mL), $PdCl_2(PPh_3)_2$ (0.1 mmol), CuI (0.05 mmol), and propargyl alcohol (1.2 mmol) were added. The mixture was stirred at 80^{O}C under nitrogen until the starting halide disappeared completely monitored by TLC. Then the reaction was quenched by saturated

NH_4Cl solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. Finally the residue was purified through column chromatography on silica gel (200-300 mesh) with hexane/EtOAc as eluent to afford the products **1a-1o** and **1q**.

3-Phenyl-prop-2-yn-1-ol (1a) [16]: 94% yield; brown oil; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.35-7.32(m, 3H), 4.50 (s, 2H), 1.75 (br, OH, 1H); IR (KBr, cm^{-1}) 3355, 3057, 2920, 2863, 1597, 1489, 1442, 1032, 952, 756, 691, 524.

3-(4-Nitro-phenyl)-prop-2-yn-1-ol (1b) [16]: 91% yield; brown solid; m.p. 95-96^{O}C;^{1}H NMR (500MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 4.56 (s, 2H), 1.83 (br, OH, 1H); IR (KBr, cm^{-1}) 3314, 3107, 3074, 2917, 2848, 1594, 1515, 1346, 1108, 1023, 949, 853, 748, 686.

4-(3-Hydroxy-prop-1-ynyl)-benzonitrile (1c)[17]: 86% yield; light yellow solid; m.p. 95-96^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 4.54 (d, *J* = 5.0 Hz, 2H), 1.96 ((t, *J* = 5.0 Hz, 1H); IR (KBr, cm^{-1}) 3456, 3124, 3065, 2236, 1712, 1604, 1503, 1424, 1362, 1032, 840, 554.

3-(4-Trifluoromethyl-phenyl)-prop-2-yn-1-ol (1d)[18]: 83% yield; brown solid; m.p.39-40^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5, 2H), 7.56 (d, *J* = 8.5, 2H), 4.54 (d, *J* = 6.0 Hz, 2H), 1.72 (t, *J* = 6.0 Hz, 1H); IR (KBr, cm^{-1}) 3322, 3050, 2925, 2867, 1616, 1406, 1324, 1168, 1127, 1068, 1018, 954, 842, 713, 597, 521.

3-(4-Chloro-phenyl)-prop-2-yn-1-ol (1e)[19]: 81% yield; yellow solid; m.p. 77-78^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 4.50 (d, *J* = 5.5 Hz, 2H), 2.51 (t, *J* = 5.5 Hz, 1H); IR (KBr, cm^{-1}) 3355, 3081, 3056, 2981, 2931, 1598, 1489, 1443, 1362, 1271, 1162, 962, 906, 755, 691.

3-(4-Bromo-phenyl)-prop-2-yn-1-ol (1f)[20]: 81% yield; brown solid; m.p.79-80^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 4.50 (s, 2H), 1.94 (br, OH, 1H); IR (KBr, cm^{-1}) 3320, 3235, 3057, 2919, 2861, 1584, 1485, 1361, 1222, 1030, 1011, 950, 822, 738, 525.

3-(4-Fluoro-phenyl)-prop-2-yn-1-ol (1g)[19]: 82% yield; colorless oil; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.43 (d, *J* = 9.0 Hz, 2H), 7.02 (t, *J* = 9.0 Hz, 2H), 4.50 (d, *J* = 5.5 Hz, 2H), 1.86 (t, *J* = 5.5 Hz, 1H); IR (KBr, cm^{-1}) 3362, 3046, 3025, 2922, 2866, 1601, 1507, 1231, 1156, 1027, 953, 836, 550.

3-(4-Methoxy-phenyl)-prop-2-yn-1-ol (1h)[16]: 59% yield; orange solid; m.p. 61-62^{O}C;^{1}H NMR (500MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.50 (d, *J* = 5.5 Hz, 2H), 3.83 (s, 3H), 1.69 (t, *J* = 5.5 Hz, 1H); IR (KBr, cm^{-1}) 3393, 3071, 3003, 2933, 2837, 1606, 1508 ,1291, 1248, 1173, 1032, 832, 525.

3-(2-Methoxy-phenyl)-prop-2-yn-1-ol (1i)[21]: 75% yield; yellow solid; m.p.48-49^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.94-6.89 (m, 2H), 4.57 (d, *J* = 6.0 Hz, 2H), 3.91 (s, 3H), 1.79 (t, *J* = 6.0 Hz, 1H); IR (KBr, cm^{-1}) 3381,3074, 3006, 2935, 2837, 1596, 1492, 1463, 1434, 1262, 1116, 1048, 1023, 795, 752.

3-(3-Methoxy-phenyl)-prop-2-yn-1-ol (1j) [18]: 70% yield; brown oil; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.24-7.21 (m, 1H),7.06-7.04 (m, 1H), 6.99 (s, 1H), 6.91-6.89 (m, 1H), 4.51 (d, *J* = 5.0 Hz, 2H), 3.80 (s, 3H), 2.20 (t, *J* = 5.0 Hz, 1H); IR (KBr, cm^{-1}) 3392, 3072, 3003, 2938, 2835, 1603, 1575, 1488, 1289, 1204, 1174, 1164, 1042, 971, 854, 782, 686.

3-(*p*-Tolyl)prop-2-yn-1-ol (1k)[18]: 78% yield; brown solid; m.p. 33-34^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 4.51 (s, 2H), 2.37 (s, 3H), 1.96 (br, OH, 1H); IR (KBr, cm^{-1}) 3364, 3025, 2923, 2854, 1713, 1605, 1508, 1456, 1377, 1029, 817, 525.

3-Biphenyl-4-yl-prop-2-yn-1-ol (1l)[22]: 81% yield; brown solid; m.p. 122-123^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.0 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.47 (t, *J* = 7.0 Hz, 2H), 7.40-7.37 (m, 1H), 4.55 (d, *J* = 5.5 Hz, 2H), 1.77(t, *J* = 5.5 Hz, 1H); IR (KBr, cm^{-1}) 3319, 3051, 3032, 2958, 2922, 2857, 1483, 1446, 1405, 1260, 1030, 1016, 952, 839, 800, 764, 722, 695, 668, 558.

3-Naphthalen-2-yl-prop-2-yn-1-ol (1m)[23]: 78% yield; yellow solid; m.p. 59-60^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.84-7.79 (m, 3H), 7.52-7.49 (m, 3H), 4.58 (s, 2H), 1.80 (br, OH, 1H); IR (KBr, cm^{-1}) 3308, 3053, 2917, 2861, 1593, 1497, 1428, 1357, 1263, 1220, 1027, 977, 861, 820, 741, 479.

3-Thiophen-3-yl-prop-2-yn-1-ol (1n)[24]: 65% yield; brown oil; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.47-7.46 (m, 1H), 7.28-7.26 (m, 1H), 7.13-7.12 (m, 1H), 4.49 (s, 2H), 2.16 (br, OH, 1H); IR (KBr, cm^{-1}) 3377, 3106, 2923, 2854, 1456, 1359, 1028, 987, 858, 783, 626.

4-Phenyl-but-3-yn-2-ol (1o)[25]:92% yield; orange oil; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H), 7.33-7.32 (m, 3H), 4.79-4.76 (m, 1H), 2.09-2.08 (m, 1H), 1.58-1.57 (m, 3H); IR (KBr, cm^{-1}) 3346, 3081, 3057, 2981, 1489, 1106, 1072, 1037, 1024, 932, 756, 691.

2-Methyl-4-phenyl-but-3-yn-2-ol (1q)[26]: 88% yield; yellow solid; m.p. 52-53^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.44-7.43 (m, 2H), 7.33-7.32 (m, 3H), 2.07 (br, OH, 1H), 1.64 (s, 6H); IR (KBr, cm^{-1}) 3362, 3081, 3056, 2981, 2931, 2868, 1598, 1573, 1489, 1443, 1362, 1271, 1162, 1070, 962, 906, 808, 755, 691, 560, 518.

*4.3. Preparation of 1**p** and 1**r***

To a solution of phenylacetylen (4 mmol) in dry THF (10 mL), n-BuLi solution (4.4 mmol) was added at -78^{O}C. The solution was allowed to warm to 0 ^{O}C over 1 hour and stirred at 0 ^{O}C for 30 minutes. Then the solution was cooled to -78^{O}C again and ketone or aldehyde (4.0 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 hour and stirred at room temperature until the ketone or aldehyde disappeared completely monitored by TLC. Then the reaction was quenched by saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. Finally the residue was purified through column chromatography on silica gel (200-300 mesh) with hexane/EtOAc as eluent to afford the products **1p** and **1r**.

1,3-Diphenyl-prop-2-yn-1-ol (1p)[27]: 79% yield; white solid; m.p. 62-63^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.52-7.50 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.36-7.34 (m, 3H), 5.72 (s, 1H), 2.51 (br, OH, 1H); IR (KBr, cm^{-1}) 3362, 3062, 3031, 1598, 1489, 1455, 1443, 1030, 997, 961, 756, 719, 691.

2,4-Diphenyl-but-3-yn-2-ol (1r)[28]: 70% yield; white solid; m.p. 91-92^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.52-7.50 (m, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.36-7.33 (m, 4H), 2.55 (br, OH, 1H), 1.90 (s, 3H); IR (KBr, cm^{-1}) 3389, 3083, 3059, 3030, 2982, 2930, 2860, 1598, 1489, 1444, 1367, 1266, 1211, 1138, 1087, 1027, 939, 756, 699, 606, 582.

*4.4. Preparation of **2a, 2d-2p**, and **3a-3e***

To a mixture of propargyl alcohol **1** (0.2 mmol) in dioxane (1 mL), $Fe(OTf)_3$ (0.04 mmol) and nucleophile (0.4 mmol) were added. The mixture was stirred at refluxing temperature until **1** disappeared completely monitored by TLC. Then the reaction was quenched by saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. Finally the residue was purified through column chromatography on silica gel (200-300 mesh) with hexane/EtOAc as eluent to afford the products **2a**, **2d-2p**, and **3a-3e**.

4-Methyl-*N*-(3-oxo-3-phenyl-propyl)-benzenesulfonamide (2a)[5]: yellow solid; m.p.86-87^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 5.27 (t, *J* = 6.5 Hz, 1H), 3.37-3.34 (m, 2H), 3.24 (t, *J* = 6.0 Hz, 2H), 2.42 (s, 3H); IR (KBr, cm^{-1}) 3288, 3062, 2923, 1682, 1597, 1449, 1325, 1217, 1158, 1092, 814, 774, 689, 665, 550.

4-Methyl-*N*-[3-oxo-3-(4-trifluoromethyl-phenyl)-propyl]-benzenesulfonamide (2d): brown solid; m.p.105-106^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H),7.74 (d, *J* = 8.0 Hz, 2H),7.31 (d, *J* = 8.0 Hz, 2H), 5.21-5.18 (m, 1H), 3.40-3.37 (m, 2H), 3.27-3.25 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 197.90, 143.54, 138.77, 137.13, 135.08, 134.80, 129.80, 128.35, 127.03, 125.78, 38.76, 36.13, 21.47; IR (KBr, cm^{-1}) 3292, 3067, 2960, 2925, 2855, 1686, 1410, 1324, 1260, 1162, 1127, 1066, 1016, 814, 661, 550. HRMS calcd for $C_{17}H_{16}F_3NNaO_3S$ $[M+Na]^+$:394.0695, found:394.0701.

***N*-[3-(4-Chloro-phenyl)-3-oxo-propyl]-4-methyl-benzenesulfonamide (2e)**[29]: brown solid; m.p. 86-87^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.21 (t, *J* = 6.5 Hz, 1H), 3.38-3.34 (m, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H); IR (KBr, cm^{-1}) 3288, 3091, 3064, 2924, 2855, 1682, 1589, 1401, 1326, 1215, 1158, 1091, 1013, 814, 661, 551.

***N*-[3-(4-Bromo-phenyl)-3-oxo-propyl]-4-methyl-benzenesulfonamide (2f)**[5]: brown solid; m.p. 122-123^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.78-7.75 (m,4H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 5.19 (t, *J* = 5.5 Hz, 1H), 3.37-3.34 (m, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H); IR (KBr, cm$^{-1)}$ 3290, 3089, 3063, 2923, 1682, 1585, 1485, 1397, 1326, 1215, 1158, 1093, 1070, 1009, 814, 661, 550.

***N*-[3-(4-Fluoro-phenyl)-3-oxo-propyl]-4-methyl-benzenesulfonamide (2g)**[29]: light yellow solid; m.p. 107-108^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 5.31 (t, *J* = 6.0 Hz, 1H), 3.36-3.32 (m, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 2.42 (s, 3H); IR (KBr, cm^{-1}) 3287, 3109, 3069, 2924, 1682, 1597, 1507, 1410, 1326, 1226, 1158, 1093, 844, 815, 662, 551.

***N*-[3-(4-Methoxy-phenyl)-3-oxo-propyl]-4-methyl-benzenesulfonamide (2h)**[15]: light yellow solid; m.p. 123-124^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5, 2H), 7.78 (d, *J* = 7.5, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 5.31 (t, *J* = 6.0 Hz, 1H), 3.89 (s, 3H), 3.36-3.32 (m, 2H), 3.18 (t, *J* = 5.5 Hz, 2H), 2.42 (s, 3H); IR (KBr, cm^{-1}) 3274, 3065, 2958, 2922, 2851, 1670, 1599, 1508, 1418, 1323, 1259, 1221, 1158, 1091, 1026, 814, 667, 550.

***N*-[3-(2-Methoxy-phenyl)-3-oxo-propyl]-4-methyl-benzenesulfonamide (2i)**: light yellow solid; m.p. 94-95^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0, 2H), 7.74 (d, *J* = 8.0, 1H), 7.52-7.49 (m,1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.03-7.00 (m,1H), 6.98 (d, *J* = 8.0 Hz, 1H), 5.23 (t, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.32-3.28 (m, 2H), 3.25 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) 200.40, 159.19, 143.22, 137.29, 134.39, 130.47, 129.69, 127.04, 126.78, 120.71, 111.69, 55.49, 43.53, 38.81,21.50; IR (KBr, cm^{-1}) 3279, 3069, 2957, 2923, 2852, 1663, 1595, 1484, 1463, 1435, 1324, 1286, 1243, 1156, 1091, 1018, 918, 813, 756, 660, 549. HRMS calcd for $C_{17}H_{19}NNaO_4S$ $[M+Na]^+$:356.0927, found: 3356.0932.

***N*-[3-(3-Methoxy-phenyl)-3-oxo-propyl]-4-methyl-benzenesulfonamide (2j)**[29]: yellow solid; m.p. 121-122^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.15-7.12 (m, 1H), 5.29 (t, *J* = 6.0 Hz, 1H), 3.87 (s, 3H), 3.37-3,33 (m, 2H), 3.22 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H); IR (KBr, cm^{-1}) 3274, 3065, 3031, 2955, 2923, 2853, 1683, 1597, 1521, 1472, 1456, 1327, 1259, 1158, 1093, 1018, 913, 799, 679, 551.

4-Methyl-*N*-(3-oxo-3-p-tolyl-propyl)-benzenesulfonamide (2k)[5]: brown solid; m.p.96-97^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.79-7.77 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.25 (t, *J* = 6.5 Hz, 1H), 3.36-3.32 (m, 2H), 3.21 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H), 2.42 (s, 3H); IR (KBr, cm^{-1}) 3275, 3062, 3030, 2923, 2868, 1678, 1607, 1418, 1324, 1287, 1181, 1160, 1093, 814, 663, 550.

***N*-(3-Biphenyl-4-yl-3-oxo-propyl)-4-methyl-benzenesulfonamide (2l)**: light yellow solid; m.p. 131-132^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.27 (t, *J* = 6.0 Hz, 1H), 3.38 (t, *J* = 5.5 Hz, 2H), 3.27 (t, *J* = 5.5 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 196.54, 146.40, 143.43, 139.65, 137.19, 134.86, 129.80, 129.02, 128.62, 128.42, 127.33, 127.28, 127.05, 38.42, 38.27, 21.52; IR (KBr, cm^{-1}) 3290, 3062, 3030, 2922, 1674, 1602, 1403, 1327, 1156, 1091, 918, 841, 762, 726, 696, 661, 548. HRMS calcd for $C_{22}H_{21}NNaO_3S$ $[M+Na]^+$:402.1134, found:402.1139.

4-Methyl-*N*-(3-naphthalen-2-yl-3-oxo-propyl)-benzenesulfonamide(2m): brown solid; m.p. 118-119^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.98-7.95 (m, 2H), 7.92-7.89 (m, 2H), 7.85 (d, *J* = 8.5 Hz, 2H),7.66-7.64 (m, 1H), 7.63-7.59 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 5.29 (t, *J* = 6.0 Hz, 1H), 3.42 (t, *J* = 5.5 Hz, 2H), 3.38 (t, *J* = 5.5 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 196.81, 143.39, 137.30, 135.83, 133.54, 132.41, 129.99, 129.77, 129.62, 128.81, 128.60, 127.82, 127.04, 126.99, 123.40, 38.50, 38.27, 21.43; IR (KBr, cm^{-1}) 3287, 3059, 2922, 2870, 1676, 1626, 1596, 1468, 1436, 1411, 1374, 1327, 1214, 1159, 1092, 924, 814, 661, 550; HRMS calcd for $C_{20}H_{19}NNaO_3S$ $[M+Na]^+$:376.0978, found:376.0984.

4-Methyl-*N*-(3-oxo-3-thiophen-3-yl-propyl)-benzenesulfonamide(2n): light yellow solid; m.p. 99-100^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.50-7.49 (m, 1H), 7.36-7.33 (m, 1H),7.32 (d, *J* = 8.0 Hz, 2H), 5.24 (t, *J*= 6.5 Hz, 1H), 3.36-3.32 (m, 2H), 3.15 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 193.10, 143.43, 141.52, 137.17, 132.62, 129.78, 127.04, 126.69, 126.58, 39.30, 38.31, 21.51; IR (KBr, cm^{-1}) 3280, 3104, 2954, 2923, 2853, 1670, 1597, 1510, 1413, 1326, 1229, 1157, 1092, 871, 813, 661, 550; HRMS calcd for $C_{14}H_{15}NNaO_3S_2$ $[M+Na]^+$: 332.0386, found: 332.0392.

4-Methyl-*N*-(1-methyl-3-oxo-3-phenyl-propyl)-benzenesulfonamide (2o)[30]: yellow solid; m.p.93-94^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.60-7.57(m, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.32-5.30 (m, 1H); 3.87-3.82 (m, 1H), 3.24-3.20

(m, 1H), 3.10-3.05 (m, 1H), 2.39 (s, 3H); IR (KBr, cm^{-1}) 3284, 3062, 2958, 2925, 2871, 1682, 1597, 1580, 1495, 1449, 1378, 1321, 1304, 1288, 1213, 1160, 1091, 1001, 901, 884, 815, 754, 689, 666, 584, 551.

4-Methyl-*N*-(3-oxo-1,3-diphenyl-propyl)-benzenesulfonamide (2p)[31]: white solid; m.p. 106-107^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.0 Hz, 2H), 7.36 (s, 1H), 7.19-7.17 (m, 6H), 5.72-5.71 (m, 1H); 4.90-4.85 (m, 1H), 3.63-3.58 (m, 1H), 3.50-3.45 (m, 1H), 2.38 (s, 3H); IR (KBr, cm^{-1})3280, 3062, 3032, 2957, 2923, 2853, 1683, 1596, 1492, 1448, 1328, 1260, 1157, 1090, 1018, 812, 749, 700, 668, 540.

***N*-(3-Oxo-3-phenyl-propyl)-benzenesulfonamide (3a)**[32]: brown solid; m.p.100-101^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.91-7.89(m, 4H), 7.62-7.57(m, 2H), 7.53 (t, *J* = 7.0 Hz, 2H), 7.48 (t, *J* = 7.0 Hz, 2H), 5.35 (br, NH, 1H), 3.38-3.36 (m, 2H), 3.26-3.24 (m, 2H); IR (KBr, cm^{-1}) 3288, 3063, 2957, 2920, 2850, 1682, 1596, 1580, 1447, 1324, 1217, 1157, 1092, 1000, 914, 819, 754, 688, 583.

4-Methoxy-*N*-(3-oxo-3-phenyl-propyl)-benzenesulfonamide (3b)[5]: yellow solid; m.p.77-78^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 5.30 (d, *J* = 6.0 Hz, 1H), 3.86 (s, 3H), 3.38-3.33 (m, 2H), 3.23 (t, *J* = 6.0 Hz, 2H); IR (KBr, cm^{-1}) 3281, 3062, 2925, 2852, 1681, 1596, 1578, 1497, 1448, 1325, 1260, 1217, 1153, 1093, 1025, 913, 833, 744, 689, 560.

4,*N*-Dimethyl-*N*-(3-oxo-3-phenyl-propyl)-benzenesulfonamide (3c)[33]: yellow solid; m.p.81-82^{O}C; ^{1}H NMR (500MHz, $CDCl_3$)δ 7.96 (d, *J* = 7.5 Hz, 2H),7.71 (d, *J* = 8.5 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 8.5 Hz, 2H), 3.48-3.45 (m, 2H), 3.37-3.34 (m, 2H), 2.83 (s, 3H), 2.45 (s, 3H); IR (KBr, cm^{-1}) 3062, 3030, 2956, 2924, 2870, 1682, 1596, 1448, 1338, 1305, 1251, 1159, 1088, 953, 815, 728, 717, 690, 548.

***N*-(3-Oxo-3-phenyl-propyl)-methanesulfonamide (3d)**[5]: yellow solid; m.p.106-107^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 5.12 (br, NH, 1H), 3.57-3.54 (m, 2H), 3.36-3.32 (m, 2H), 3.01 (s, 3H); IR (KBr, cm^{-1}) 3294, 3060, 3025, 2920, 2850, 1682, 1596, 1448, 1391, 1217, 1148, 970, 755, 690, 521.

***N*-(3-Oxo-3-phenyl-propyl)-benzamide (3e)**[34]: yellow solid; m.p.92-93^{O}C;^{1}H NMR (500MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.51-7.48(m, 3H), 7.43 (t, *J* = 7.5 Hz, 2H), 6.98 (br, NH, 1H), 3.93-3.90 (m, 2H), 3.39-3.35 (m, 2H); IR (KBr, cm^{-1}) 3337, 3061, 3029, 2956, 2926, 2854, 1682, 1643, 1578, 1535, 1488, 1448, 1326, 1307, 1215, 1076, 1001, 971, 801, 712, 690.

4.5. Procedure for the synthesis of ***racemic Fluoxetine***

To a mixture of **3c** (1 mmol) in methanol (3 mL) $NaBH_4$ (1.2 mmol) was added, and the mixture was stirred at room temperature until the **3c** disappeared completely monitored by TLC. Then the reaction was quenched by saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude **4**. 60% sodium hydride (1.3 mmol) was added to a mixture of crude **4** (1 mmol) in DMSO (6 mL). After stirring this mixture for 1 hour at 60 ^{O}C, a solution of 4-chlorobenzotrifluoride (2 mmol) in DMSO (3 mL) was added and the reaction was stirred at 100^{O}C until the **4** disappeared completely monitored by TLC.Then the reaction was quenched by saturated NH_4Cl solution and extracted with ethyl acetate. The combined organicphases were washed with brine, dried over anhydrous Na_2SO_4 andconcentrated under reduced pressure to give a residue. Finally the residue was purified through column chromatography on silica gel (200-300 mesh) with hexane/EtOAc as eluent to afford **5** in 72% yield after 2 steps.

To a dried three neck round bottom flash sodium metal (21.5 mmol), naphthalene (28 mmol) and dry glycol dimethyl ether (10 mL) were added and the reaction mixture was stirred at room temperature for 2 hours. Then the naphtalenide mixture was added slowly to a solution of **5** (0.72 mmol) in dry glycol dimethyl ether (4 mL). The reaction was stirred at room temperature until **5** disappeared completely monitored by TLC. The reaction was quenched with couple drops of water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. Finally, the residue was purified through column chromatography on silica gel (200-300 mesh) with hexane/EtOAc as eluent to afford racemic fluoxetine in 88% yield. **Racemic fluoxetine**[14]: brown solid; m. p. 157-158^{O}C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.40-7.37 (m, 4H), 7.33-7.32 (m, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.78-4.76 (m, 1H), 3.56-3.53 (m, 2H), 3.00 (s, 3H), 2.05-2.01 (m, 2H); IR (KBr, cm^{-1}) 3365, 3064, 3031, 2923, 2853, 1616, 1533, 1457, 1328, 1199, 1107, 1069, 818, 701, 592.

4.6. Procedure for the synthesis of ***6***

To a mixture of propargyl alcohol **1a** (0.2 mmol) in dioxane (1 mL), $Fe(OTf)_3$ (0.2 mmol) was added, and the reaction was stirred at refluxing temperature until **1a** disappeared completely monitored by TLC. Then the reaction was quenched by saturated $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. Finally the residue was purified through column chromatography on silica gel (200-300 mesh) with hexane/EtOAc as eluent to give **6**. **2-Methylene-1,5-diphenyl-pentane-1,5-dione (6)**[35]**:** yellow solid; m.p.56-57^{O}C; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.50-7.45 (m, 2H), 7.41-7.34 (m, 4H), 5.89 (s, 1H), 5.61 (s, 1H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.85 (t, *J* = 7.2 Hz, 2H); IR (KBr, cm^{-1}) 3083, 3059, 3026, 2960, 2921, 2850, 1684, 1653, 1595, 1447, 1261, 1206, 1095, 1023, 1001, 799, 750, 708, 690.

Acknowledgments

The work was supported by National Natural Science Foundation of China (Grant No.21502117), and Shanghai Municipal Education Commission (Plateau Discipline Construction Program). Support from Prof. Guanjun Wang and Prof. Gang Zhao was also greatly appreciated.

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Supplementary Material

^{1}H NMR spectra, ^{13}C NMR spectra of new compounds, and HRMS spectra of new compounds associated with this article can be found, in the online version, at http://dx.doi.org.