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A microwave-enhanced, solventless Mannich condensation of terminal alkynes and secondary amines with *para*-formaldehyde on cuprous iodide doped alumina

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Abstract—A microwave-enhanced, solventless Mannich condensation of terminal alkynes and secondary amines with *para*-formaldehyde on cuprous iodide doped alumina has been developed. β-Aminoalkynes are generated in good yields. The reaction can be extended to include a cyclization, which affords 2-substituted benzo[*b*]furans. The chemoselectivity of the reaction indicates that terminal alkynes are much more reactive than enolizable ketones under the reaction conditions.

1. Introduction

The Mannich reaction is a classic example of a three-component condensation reaction.[1] In general, formaldehyde (or *para*-formaldehyde), an amine, and an 'active-hydrogen' component such as an enolizable ketone or terminal alkyne are allowed to react to afford the corresponding β-aminoketone or β-aminoalkyne. The latter Mannich adduct contains at least two potential sites for further modification: the amine and the alkyne.[2] In addition, β-aminoalkynes and their derivatives have a wide range of applications including use as pharmaceutical intermediates[3] and as general synthetic building blocks.[4] Moreover, the alkyne moieties may be functionalized in various ways.

The traditional Mannich method for synthesizing β-aminoalkynes often requires drastic reaction conditions and generally is run in dioxane, a toxic solvent. The organic solvent and the metal catalyst can be difficult to handle and often difficult to dispose of safely.

We have found alumina to be a particularly useful reagent in organic synthesis because it can be modified in a variety of ways that enhance its reactivity. It also obviates a number of environmental problems.[5] For example, using a commercially available alumina/potassium fluoride mixture to which palladium powder was added, we were able to carry out Suzuki and Sonogashira coupling reactions on a wide variety of aromatic moieties without the use of solvents.[6]

Microwave irradiation of organic reactions has gained in popularity in recent years since it was found to accelerate a wide variety of transformations.[7] Early experiments utilized solvents with high dielectric constants, which permitted rapid heating of the reaction solution. In recent years, a number of reports have appeared in which reactants are coated on to surfaces, which themselves absorb little or no microwave energy; in these instances, the reactive species absorb the microwave energy but the temperature of the reaction mixture tends to rise only modestly. This results in relatively large energy saving as well as making it possible to carry out reactions in relatively simple glassware such as open beakers and flasks.[8]

We now wish to report the details of a microwave-enhanced Mannich condensation of terminal alkynes with amines and *para*-formaldehyde on CuI-doped alumina in the absence of solvents that produces the corresponding aminomethylated adducts in good yields. The reaction can be extended to a Mannich condensation cyclization sequence that generates 2-substituted benzo[*b*]furans in one-pot and in good yields. The process is highly efficient, does not require pre-forming the iminium species, and is not hampered by the heterogeneity of the reaction medium (Scheme 1).

$$R^1C{\equiv}CH + (CH_2O)_n + HNR^2R^3 \xrightarrow[MW]{CuI/Al_2O_3} R^1C{\equiv}CCH_2NR^2R^3$$

Scheme 1.

Keywords: Cuprous salts; Mannich reaction; Solventles; Microwave.
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Table 1. A Effect of cuprous salts on the Mannich condensation[a]

Entry	Cuprous salt	Yield (%)[b]
a	Cu_2Cl_2	28
b	CuBr	26
c	CuI	82
d	None	0

[a] Reaction conditions: dibenzylamine (1.00 mmol), 1-decyne (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous salt (3.00 mmol), Al_2O_3 (1.00 g), irradiated at 300 W for 10 min.
[b] Isolated yields.

2. Results and discussion

2.1. Effect of cuprous salts on the Mannich condensation of terminal alkynes with amines and *para*-formaldehyde

We initially explored the affect of the cuprous salts on the Mannich condensation of terminal alkynes with amines and *para*-formaldehyde. The results are listed in Table 1. Dibenzylamine, *para*-formaldehyde and 1-decyne were chosen as the model reactants for this investigation.

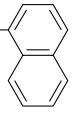
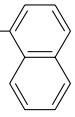
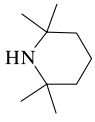
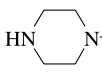
It is evident that the Mannich reaction requires a cuprous salt to 'active' the terminal alkyne carbon–hydrogen bond to promote aminomethylation. Among the cuprous salts we tested, cuprous iodide was most effective and was chosen for further study.

2.2. Mannich condensation of terminal alkynes with secondary amines and *para*-formaldehyde

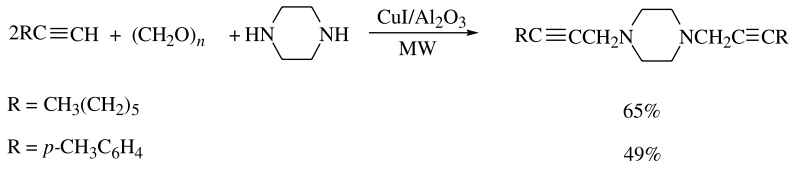
Table 2 contains a summary of the experimental results. A number of terminal alkynes were successfully condensed with secondary amines and *para*-formaldehyde in good yields. Dibenzylamine, methylbenzylamine, morpholine, piperidine, 1-phenylpiperazine, *N*-methyl-1-naphthalene-methylamine, di(*iso*-propyl)amine all reacted smoothly with terminal alkynes and *para*-formaldehyde to generate the corresponding Mannich products. It should be noted that the reaction tolerated many functional groups and that the sterically hindered 2,2,6,6-tetramethylpiperidine smoothly produced the corresponding Mannich adduct.

During the investigation, we found that piperazine reacts with terminal alkynes (2 equiv) and *para*-formaldehyde (excess) to afford the diaminomethylation adducts [bis-(β-aminoalkyne)] (Scheme 2) and 1,9-decadiyne reacted with secondary amines (2 equiv) and *para*-formaldehyde (excess) to generate the bis-Mannich products in moderate to good yields (Scheme 3).

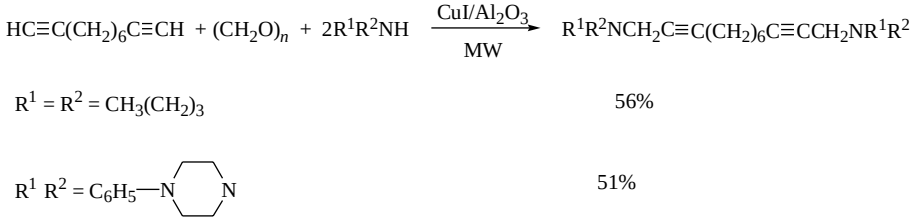
Table 2. Mannich condensation reaction of terminal alkynes with secondary amine and *para*-formaldehyde[a]

Entry	Alkyne	Amine	Product	Yield (%)[b]
a	n-$C_8H_{17}C{\equiv}CH$	$(n\text{-}C_4H_9)_2NH$	n-$C_8H_{17}C{\equiv}CCH_2N(n\text{-}C_4H_9)_2$	88
b	n-$C_8H_{17}C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	n-$C_6H_{13}C{\equiv}CCH_2N(CH_2CH_6H_5)_2$	82
c	n-$C_6H_{13}C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	n-$C_8H_{17}C{\equiv}CCH_2(CH_2C_6H_5)_2$	81
d	n-$C_8H_{17}C{\equiv}CH$	$C_6H_5CH_2NHCH_3$	n-$C_8H_{17}C{\equiv}CCH_2N(CH_3)CH_2C_6H_5$	89
e	n-$C_8H_{17}C{\equiv}CH$		n-$C_8H_{17}C{\equiv}CCH_2N$ 	82
f	n-$C_8H_{17}C{\equiv}CH$	CH_3NHCH_2 	n-$C_8H_{17}C{\equiv}CCH_2N(CH_3)CH_2$ 	71
g	$C_6H_5C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	$C_6H_5C{\equiv}CCH_2N(CH_2C_6H_5)_2$	79
h	$C_6H_5C{\equiv}CH$		$C_6H_5C{\equiv}CCH_2N$ 	88
i	p-$CH_3C_6H_4C{\equiv}CH$		p-$CH_3C_6H_4C{\equiv}CCH_2N$ 	80
j	p-$CH_3C_6H_4C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	p-$CH_3C_6H_4C{\equiv}CCH_2N(CH_2C_6H_5)_2$	83
k	p-$CH_3C_6H_4C{\equiv}CH$		p-$CH_3C_6H_4C{\equiv}CCH_2N$ 	92
l	p-$CH_3C_6H_4C{\equiv}CH$		p-$CH_3C_6H_4C{\equiv}CCH_2N$ 	74
m	p-$FC_6H_4C{\equiv}CH$		p-$FC_6H_4C{\equiv}CCH_2N$ 	90
n	p-$FC_6H_4C{\equiv}CH$	$(C_6H_5CH_2)_2NH$	p-$FC_6H_4C{\equiv}CCH_2N(CH_2C_6H_5)_2$	85
o	o-$FC_6H_4C{\equiv}CH$		o-$FC_6H_4C{\equiv}CCH_2N$ 	72
p	p-$BrC_6H_4C{\equiv}CH$	$(n\text{-}C_4H_9)_2NH$	p-$BrC_6H_4C{\equiv}CCH_2N(n\text{-}C_4H_9)_2$	89

[a] Reaction conditions: secondary amine (1.00 mmol), terminal alkyne (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous iodide (3.00 mmol), Al_2O_3 (1.00 g).
[b] Isolated yields.



Scheme 2.



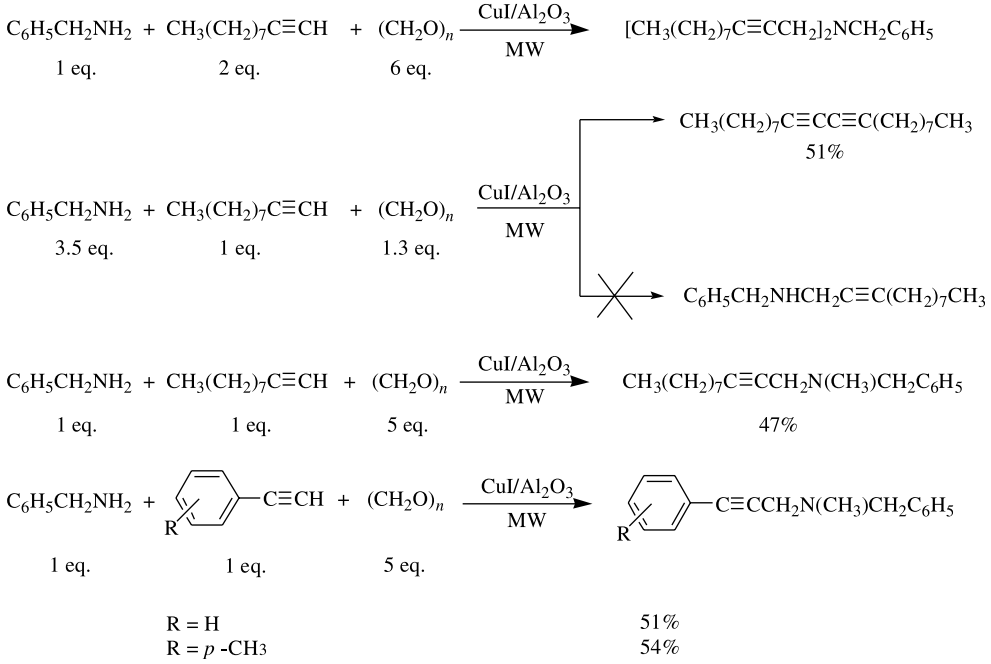
Scheme 3.

2.3. Mannich condensation of terminal alkynes with primary amines and *para*-formaldehyde

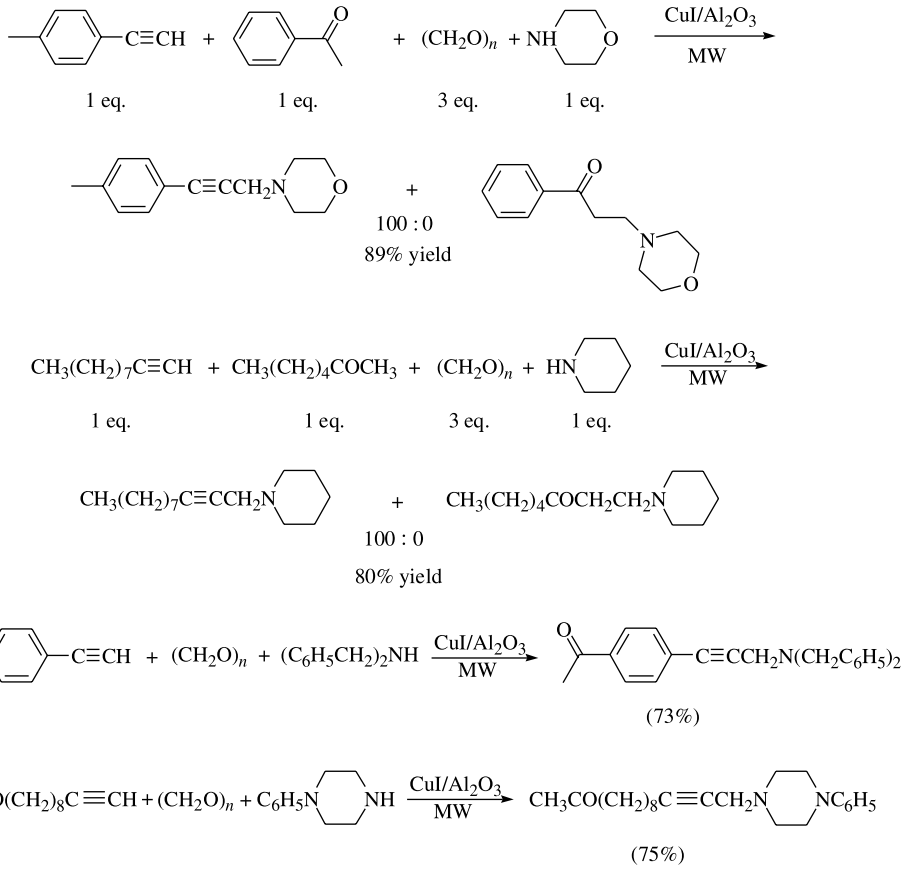
As anticipated, benzylamine (1 equiv), a primary amine, reacted with 1-decyne (2 equiv) and *para*-formaldehyde (6 equiv) to produce the bis-Mannich condensation because there are two nitrogen–hydrogen bonds in the primary amine (Scheme 4). Interestingly, when the ratio of reactants is changed alternative reations occur. For example, benzylamine (1 equiv) reacted with 1-decyne (1 equiv) and *para*-formaldehyde (5 equiv) to generate the Mannich condensation product followed reductive methylation (Scheme 4) phenylacetylene derivatives also afforded methylation products in fair yields (Scheme 4). The reaction provides an alternative route to *N*-methyl-β-aminoalkynes in a convenient and straightforward fashion.[9]

2.4. The chemoselectivity of the Mannich condensation of terminal alkynes with secondary amines and *para*-formaldehyde

The chemoselectivity of the reaction was investigated. When a mixture of acetophenone and 4-ethynyltoluene (or a mixture of 1-decyne and 2-heptanone) served as competitive acidic substrates for the Mannich reaction, only the β-aminoalkynes were formed (Scheme 5). As anticipated, the Mannich reaction of 4-acetyl-1-ethynylbenzene with dibenzylamine and *para*-formaldehyde (or 11-dodecyn-2-one



Scheme 4.



Scheme 5.

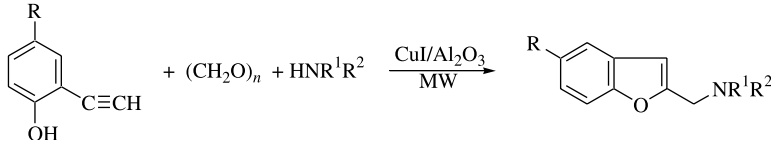
with 1-phenylpiperazine and *para*-formaldehyde) generated β-aminoalkyne products exclusively (Scheme 5).

2.5. 2-Subsitituted benzo[*b*]furans from the Mannich condensation of *o*-ethynylphenol with secondary amines and *para*-formaldehyde

Benzo[*b*]furans and their derivatives have received much attention in recent years because of their occurrence in natural products and their physiological activity.[10] They are widely used as antitumor agents,[11] as ligands of the adenosine A_1 receptor,[12] and as calcium entry blockers.[13] General routes to benzo[*b*]furans involve reductive cyclization of ketoesters by low-valent titanium,[14] photochemically induced rearrangement of phosphate esters,[15] palladium catalyzed Suzuki coupling of boronic acids with organic halides or triflates,[16] and palladium catalyzed Sonogashira coupling (followed by cyclization) of *o*-iodophenol and terminal alkynes.[17] No report has appeared describing the synthesis of 2-substituted benzo[*b*]furans using a Mannich condensation reaction.

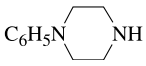
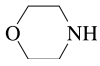
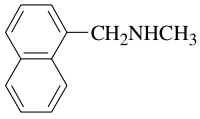
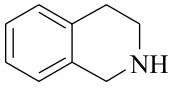
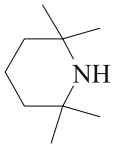
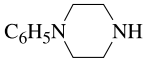
The Mannich condensation–cyclization of *o*-ethnylphenol with secondary amines and *para*-formaldehyde on cuprous iodide doped alumina under solvent free and microwave irradiation conditions generates 2-(dialkylaminomethyl)-benzo[*b*]furans in good yields (Scheme 6 and Table 3).

Table 3 contains a summary of the results. Under microwave irradiation and solvent free conditions, *o*-ethynylphenol (as well as *p*-acetyl-*o*-ethynylphenol) reacts smoothly with *para*-formaldehyde and a variety of secondary amines, such as 1-phenylpiperizine, piperdine, morpholine, dibutylamine, di(*iso*-propyl)amine, and *N*-methylaniline, methylbenzylamine, 1,2,3,4-tetrahydroisoquioine, and *N*-methylnaphthylmethylamine to afford the desired 2-substituted benzo[*b*]furans in one-pot. It should be noted that the highly sterically encumbered 2,2,6,6-tetramethylpiperidine also smoothly undergoes the reaction to generate the corresponding 2-substituted-benzo[*b*]furan, which was characterized by ^{1}H, ^{13}C NMR, MS and microanalysis, and confirmed by X-ray crystal diffraction. Interestingly, when *o*-ethynylphenol (2 equiv) was allowed



Scheme 6.

Table 3. Mannich condensation–cyclization reaction of *o*-ethnylphenol and its deriatives with secondary amines and *para*-formaldehyde (see Scheme 6)[a]

Entry	R	Amine	Yield (%)[b]
a	H		65
b	H	$(n\text{-}C_4H_9)_2NH$	68
c	H		65
d	H	$CH_5CH_2NHCH_3$	62
e	H		55
f	H		70
g	H		59
h	H	$(i\text{-}C_3H_7)_2NH$	56
i	H		52
j	H	$C_6H_5NHCH_3$	36
k	H		65

[a] Reaction condition: secondary amine (1.00 mmol), *o*-ethynylphenol (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous iodide (3.00 mmol), Al_2O_3 (1.00 g), irradiated at 300 W for 10 min.
[b] Isolated yields.

to react with *para*-formaldehyde (excess) and piperazine (1 equiv), a bis-Mannich condensation cyclization product was formed (Scheme 7).

2.6. Surface recyclability

We utilized a surface containing 3 mmol of cuprous iodide per gram of alumina for 1 mmol scale reactions. In an effort to enhance the efficiency of the new solid-state Mannich condensation reaction and reduce waste, recycling was investigated. Table 4 contains a summary of the results. It can be seen that the catalyst and alumina remain active through at least eight cycles. After the product was removed from the surface using an organic solvent, the surface was used directly for the next trial without further treatment.

Table 4. Successive trials for Mannich condensation using CuI/Al_2O_3[a]

Trial	Yield (%)[b]
1	82
2	80
3	81
4	79
5	80
6	82
7	80
8	79

[a] Experiment were carried out as described in the Section 4 by using 1-decyne (1 mmol), dibenzylamine (1.00 mmol), *para*-formaldehyde (3.00 mmol), cuprous iodide (3.00 mmol), Al_2O_3 (1.00 g), microwave irradiation at 300 W for 10 min.
[b] Isolated yields.

3. Conclusion

A reliable, rapid, practical, and environmentally benign method for the synthesizing β-aminoalkynes and 2-substituted benzo[*b*]furans has been developed, which involves the use of a solvent-free mixture of cuprous iodide and alumina under microwave irradiation conditions. The process is highly efficient, does not require pre-forming the iminium species, and is not hampered by the heterogeneity of the reaction.

4. Experimental

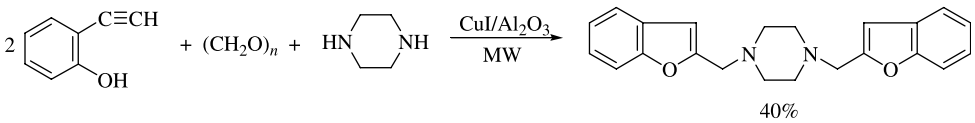
Melting points were recorded on a MEL-TEMP melting point apparatus and are uncorrected. IR were recorded on a Bomem MB 100 FT-IR. All ^1H and ^{13}C NMR spectra were recorded on a 250 MHz Bruker AC 250 or Avance 400 MHz spectrometer. Chemical shift are given as δ value with reference to tetramethylsilane (TMS) as internal standard. GC/MS data were obtained by using a Hewlett-Packard 6890 series GC equipped with a 5973 mass selective detector. Microanalyses were performed by Atlantic Microlabs, Norcross, GA. A commercially available Ethos E Touch Control microwave unit (Milestone) was utilized.

Al_2O_3 and cuprous iodide were purchased from Aldrich Chemical Co. The organic reagents were analytical grade and used as received (Aldrich Chemical Co.).

Products were purified, if applicable, by flash chromatography on 230–400 mesh ASTM 60 Å silica gel, SiO_2.

4.1. General procedure for Mannich condensation of terminal alkynes with amines and *para*-formaldehyde

Secondary amine (1.00 mmol) and terminal alkyne (1.00 mmol) were added to a mixture of cuprous iodide (0.572 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol)



Scheme 7.

and alumina (1.00 g) contained in a clean, dry, 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle to serve as a pressure release valve), placed in the microwave oven and irradiated at 300 W for 10 min [caution: heating volatile materials in commercial microwave ovens for extended periods can be hazardous]. After cooling, ether (4 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was vacuum filtered using a sintered glass funnel and the product was purified by flash chromatography to yield the desired β-aminoalkyne.

4.1.1. Dibutyl(undec-2-ynyl)amine.[18] Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.35 (s, 2H), 2.38–2.49 (t, 4H), 2.12–2.21 (t, 3H), 1.19–1.60 (m, 20H), 0.88–0.94 (m, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 84.9, 74.7, 53.5, 42.3, 31.7, 29.7, 29.2, 29.1, 29.0, 28.8, 22.7, 20.7, 18.7, 14.1.

4.1.2. Dibenzyl(undec-2-ynyl)amine. Oil; IR (film, $CHCl_3$) 2261 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.16 (m, 10H), 3.65 (s, 2×2H), 3.22 (s, 2H), 2.24 (t, J=6.6 Hz, 2H), 1.55–1.30 (m, 12H), 0.88 (t, J=6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 139.1, 128.9, 128.1, 126.9, 85.7, 74.4, 57.5, 41.6, 31.8, 29.3, 29.1, 28.9, 22.6, 18.7, 14.1; MS *m/z* (relative intensity) 347 (M^+, 3), 270 (6), 256 (10), 194 (7), 91 (100). Anal. Calcd for $C_{25}H_{33}N$: C, 86.40; H, 9.57; N, 4.03. Found: C, 86.34; H, 9.68; N, 4.09.

4.1.3. Dibenzyl(non-2-ynyl)amine. Oil; IR (film, $CHCl_3$) 2260 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.18 (m, 10H), 3.65 (s, 2×2H), 3.22 (s, 2H), 2.25 (t, J=6.7 Hz, 2H), 1.59–1.31 (m, 8H), 0.91 (t, J=6.7 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 139.1, 129.0, 128.2, 126.9, 85.8, 74.4, 57.5, 41.6, 31.4, 29.1, 28.6, 22.6, 18.7, 14.1; MS *m/z* (relative intensity) 319 (M^+, 3), 242 (7), 228 (9), 194 (6), 91 (100). Anal. Calcd for $C_{23}H_{29}N$: C, 86.47; H, 9.15; N, 4.38. Found: C, 86.24; H, 9.22; N, 4.41.

4.1.4. Benzylmethyl(undec-2-ynyl)amine. Oil; IR (film, $CHCl_3$) 2261 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34–7.21 (m, 5H), 3.55 (s, 2H), 3.25 (s, 2H), 2.30 (s, 3H), 2.23 (t, J=6.8 Hz, 2H), 1.56–1.28 (m, 12H), 0.88 (t, J=6.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.6, 129.1, 128.1, 127.0, 85.7, 74.5, 60.1, 45.4, 41.7, 31.8, 29.2, 29.0, 28.9, 28.8, 22.6, 18.7, 14.0; MS *m/z* (relative intensity) 271 (M^+, 7), 194 (26), 158 (21), 120 (19), 91 (100). Anal. Calcd for $C_{19}H_{29}N$: C, 84.07; H, 10.77; N, 5.16. Found: C, 84.21; H, 10.88; N, 5.23.

4.1.5. 1-(Undec-2-ynyl)piperidine. Oil; IR (film, $CHCl_3$) 2188 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.20 (t, J=1.8 Hz, 2H), 2.47 (s, br, 2×2H), 2.18 (t, J=6.8 Hz, 2H), 1.66–1.28 (m, 18H), 0.88 (t, J=6.5 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 84.9, 75.0, 53.1, 47.9, 31.6, 29.0, 28.9, 28.7, 25.7, 23.8, 22.4, 18.5, 13.8; MS *m/z* (relative intensity) 235 (M^+, 22), 234 (M^+-1, 74), 150 (30), 136 (59), 122 (58), 98 (23), 84 (100). Anal. Calcd for $C_{16}H_{29}N$: C, 81.63; H, 12.42; N, 5.95. Found: C, 81.45; H, 12.55; N, 6.02.

4.1.6. Methyl-1-(naphthalenemethyl)(undec-2-ynyl)-amine. Oil; IR (film, $CHCl_3$) 2259 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.29 (d, J=8.1 Hz, 1H), 7.82–7.73 (m, 2H), 7.52–7.34 (m, 4H), 3.96 (s, 2H), 3.30 (s, 2H), 2.34 (s, 3H), 2.26 (t, J=6.7 Hz, 2H), 1.62–1.28 (m, 12H), 0.87 (t, J=6.6 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 134.5, 133.8, 132.6, 128.3, 128.0, 127.5, 125.8, 125.5, 125.0, 124.6, 85.9, 74.7, 58.1, 45.6, 41.9, 31.8, 29.2, 29.0, 28.9, 22.6, 18.8, 14.1; MS *m/z* (relative intensity) 321 (M^+, 5), 306 (1), 208 (17), 180 (50), 141 (100), 115 (19). Anal. Calcd for $C_{23}H_{31}N$: C, 85.92; H, 9.72; N, 4.36. Found: C, 85.84; H, 9.90; N, 4.44.

4.1.7. Dibenzyl(3-phenylprop-2-ynyl)amine.[19] Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.18 (m, 15H), 3.72 (s, 4H), 3.43 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.8, 131.7, 129.0, 128.3, 127.9, 127.1, 123.4, 85.9, 84.4, 57.9, 42.0.

4.1.8. 1-(3-phenylprop-2-ynyl)piperidine.[20] Oil; IR (film, $CHCl_3$) 2188 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.45–7.41 (m, 2H), 7.27–7.25 (m, 3H), 3.46 (s, 2H), 2.55 (s, br, 2×2H), 1.67–1.59 (m, 2×2H), 1.45 (t, J=5.5 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 131.4, 127.9, 127.7, 123.1, 84.8, 84.7, 53.2, 48.2, 25.7, 23.7; MS *m/z* (relative intensity) 199 (M^+, 42), 170 (11), 157 (25), 130 (7), 122 (13), 115 (100).

4.1.9. 1-[3-(*p*-Tolyl)prop-2-ynyl]piperidine.[21] Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34–7.30 (d, 2H), 7.11–7.07 (d, 2H), 3.46 (s, 2H), 2.50–2.61 (t, 3H), 2.32 (s, 3H), 1.59–1.70 (t, 4H), 1.36–1.48 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 137.7, 131.5, 128.8, 120.2, 85.0, 84.2, 53.4, 48.4, 25.9, 23.7, 21.3.

4.1.10. Dibenzyl[3-(*p*-tolyl)prop-2-ynyl]amine. Oil; IR (film, $CHCl_3$) 2229 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.44–7.20 (m, 12H), 7.11 (d, J=7.9 Hz, 2H), 3.74 (s, 2×2H), 3.45 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.9, 138.0, 131.6, 129.0, 128.2, 127.0, 120.3, 86.0, 83.6, 57.7, 42.0, 21.4; MS *m/z* (relative intensity) 325 (M^+, 6), 234 (11), 194 (9), 129 (45), 91 (100). Anal. Calcd for $C_{24}H_{23}N$: C, 88.57; H, 7.12; N, 4.30. Found: C, 88.45; H, 7.21; N, 4.27.

4.1.11. 4-[(3-*p*-Tolyl)prop-2-ynyl]morpholine. Oil; IR (film, $CHCl_3$) 2204 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.32 (d, J=8.1 Hz, 2H), 7.09 (d, J=8.0 Hz, 2H), 3.75 (t, J=4.7 Hz, 2×2H), 3.48 (s, 2H), 2.62 (t, J=4.6 Hz, 2×2H), 2.32 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.0, 131.4, 128.9, 119.8, 85.5, 83.2, 66.7, 52.3, 47.9, 21.3; MS *m/z* (relative intensity) 215 (M^+, 29), 184 (32), 170 (26), 157 (40), 129 (100). HRMS Calcd for $C_{14}H_{17}NO$: 215.1310, found: 215.1310.

4.1.12. 2,2,6,6-Tetramethyl-1-[3-(*p*-tolyl)prop-2-ynyl]-piperdine. Mp 178–180 °C; IR (KBr, $CHCl_3$) 2401 cm^{-1} (C≡C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.27 (d, J=7.9 Hz, 2H), 7.06 (d, J=7.8 Hz, 2H), 3.55 (s, 2H), 2.31 (s, 3H), 1.54–1.44 (m, 6H), 1.17 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 137.3, 131.3, 128.8, 121.2, 92.2, 81.0, 54.9, 41.2, 33.8, 27.5, 21.4, 17.8; MS *m/z* (relative intensity) 269 (M^+, 2),

254 (7), 129 (100). Anal. Calcd for $C_{19}H_{27}N$: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.56; H, 10.23; N, 5.11.

4.1.13. 1-[3-(4-Fluorophenyl)prop-2-ynyl]-4-phenylpiperazine. Mp 80.5–81.5 °C; IR (KBr) 2253 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.44–7.38 (m, 2H), 7.29–7.23 (m, 2H), 7.01–6.83 (m, 5H), 3.55 (s, 2H), 3.25 (t, $J=4.8$ Hz, 2×2H), 2.78 (t, $J=4.8$ Hz, 2×2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.3, 160.3, 151.1, 133.6, 133.4, 129.0, 119.7, 119.0 (d, $J=3.3$ Hz), 116.1, 115.6, 115.2, 84.4, 83.9, 52.0, 49.0, 47.6; MS *m/z* (relative intensity) 294 (M^+, 12), 252 (6), 188 (11), 176 (14), 159 (100), 133 (84), 106 (60). Anal. Calcd for $C_{19}H_{19}N_2F$: C, 77.52; H, 6.51; N, 9.52. Found: C, 77.60; H, 6.66; N, 9.55.

4.1.14. Dibenzyl[(3-*p*-fluorophenyl)prop-2-ynyl]amine.[22] Oil; ^1H NMR (250 MHz, $CDCl_3$): δ 7.44–7.01 (m, 14H), 3.74 (S, 2×2H), 3.46 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 164.3, 160.4, 138.8, 129.9, 129.8, 129.0, 128.3, 127.6, 127.2, 125.2, 118.7, 118.4, 115.5, 115.2, 85.6, 84.7, 57.8, 41.9.

4.1.15. 4-[3-(2-Fluorophenyl)prop-2-ynyl)]morpholine. Oil; IR (film, $CHCl_3$) 2205 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.46–7.39 (m, 1H), 7.33–7.24 (m, 1H), 7.10–7.02 (m, 2H), 3.77 (t, $J=4.6$ Hz, 2×2H), 3.56 (s, 2H), 2.66 (s, br, 2×2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 162.8 (d, $J=250.3$ Hz), 133.4, 129.8 (d, $J=7.6$ Hz), 123.8 (d, $J=3.4$ Hz), 115.3 (d, $J=20.8$ Hz), 111.4 (d, $J=15.4$ Hz), 89.3, 78.9, 66.8, 52.2, 48.0; MS *m/z* (relative intensity) 219 (M^+, 16), 188 (17), 161 (16), 133 (100), 86 (26). Anal. Calcd for $C_{13}H_{14}NFO$: C, 71.21; H, 6.44; N, 6.39. Found: C, 70.93; H, 6.50; N, 6.28.

4.1.16. [3-(4-Bromophenyl)prop-2-ynyl]dibutylamine. Oil; IR (film, $CHCl_3$) 2190 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.41 (d, $J=8.5$ Hz, 2H), 7.27 (d, $J=8.5$ Hz, 2H), 3.58 (s, 2H), 2.51 (t, $J=7.3$ Hz, 2×2H), 1.51–1.27 (m, 8H), 0.93 (t, $J=7.1$ Hz, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 133.0, 131.3, 122.3, 121.9, 86.2, 83.8, 53.6, 42.6, 29.6, 20.6, 14.0; MS *m/z* (relative intensity) 323, 321 (M^+, 4, 4), 280, 278 (97, 100), 195, 193 (78, 79), 114 (26), 84 (20). Anal. Calcd for $C_{17}H_{24}NBr$: C, 63.36; H, 7.51; N, 4.35. Found: C, 63.31; H, 7.53; N, 4.37.

4.2. General procedure for the Mannich condensation of terminal alkyne with piperazine and *para*-formaldehyde

Terminal alkyne (2.00 mmol), *para*-formaldehyde (6.00 mmol) and piperazine (1.00 mmol) were mixed well with Al_2O_3 (2.00 g) and cuprous iodide (1.16 g, 6.00 mmol) and placed in the microwave oven and irradiated at 30% power for 10 min.

4.2.1. 1,4-Di(non-2-ynyl)piperazine. Oil; IR (film, $CHCl_3$) 2196 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$): 3.25 (s, 2×2H), 2.62 (s, br, 4×2H), 2.17 (t, $J=6.9$ Hz, 2×2H), 1.52–1.26 (m, 16H), 0.89 (t, $J=6.7$ Hz, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 85.3, 74.5, 51.7, 47.1, 31.1, 28.6, 28.4, 22.3, 18.5, 13.8; MS *m/z* (relative intensity) 330 (M^+, 3), 287 (10), 260 (9), 231 (10), 207 (100), 178 (26), 108 (20). Anal. Calcd for $C_{22}H_{38}N_2$: C, 79.94; H, 11.59; N, 8.47. Found: C, 76.69; H, 11.68; N, 8.43.

4.2.2. 1,4-Di[3-(*p*-tolyl)prop-2-ynyl]piperazine. Mp 119–121 °C; IR (film, $CHCl_3$) 2199 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$) 7.32 (d, $J=8.0$ Hz, 2×2H), 7.08 (d, $J=8.1$ Hz, 2×2H), 3.52 (s, 2×2H), 2.74 (s, br, 2×4H), 2.32 (s, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.0, 131.5, 128.9, 120.0, 85.4, 83.5, 51.9, 47.6, 21.3; MS *m/z* (relative intensity) 342 (M^+, 2), 341 (M^+-1, 5), 272 (3), 223 (5), 213 (11), 129 (100), 115 (8). Anal. Calcd for $C_{24}H_{26}N_2$: C, 84.17; H, 7.65; N, 8.18. Found: C, 83.96; H, 7.85; N, 8.03.

4.3. General procedure for the Mannich condensation of α,ω-dialkyne with secondary amine and *para*-formaldehyde

α,ω-Dialkyne (1.00 mmol), *para*-formaldehyde (6.00 mmol) and secondary amine (2.00 mmol) were mixed well with Al_2O_3 (2.00 g) and cuprous iodide (1.16 g, 6.00 mmol) and placed in the microwave oven and irradiated at 300 W for 10 min.

4.3.1. *N,N,N,N*-Tetrabutyl-2,10-dodecadiynyl-1,12-diamine. Oil; IR (film, $CHCl_3$) 2189 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$) 3.34 (t, $J=1.9$ Hz, 2×2H), 2.43 (t, $J=7.3$ Hz, 4×2H), 2.19 (t, $J=6.5$ Hz, 2×2H), 1.53–1.25 (m, 24H), 0.92 (t, $J=7.1$ Hz, 4×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 84.5, 74.7, 53.3, 42.0, 29.5, 28.7, 28.1, 20.6, 18.5, 13.9; MS *m/z* (relative intensity) 246 (M^+-170, 21), 112 (12), 84 (100), 70 (29), 57 (66). Anal. Calcd for $C_{28}H_{52}N_2$: C, 80.70; H, 12.58; N, 6.72. Found: C, 80.50; H, 12.62; N, 6.69.

4.3.2. 1,12-Di(4-phenylpiperazino)-2,10-dodecadiyne. Mp 81–82 °C; IR (film, $CHCl_3$) 2204 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$) 7.28–7.21 (m, 2×2H), 6.93–6.81 (m, 2×3H), 3.29 (s, 2×2H), 3.22 (t, $J=7.7$ Hz, 4×2H), 2.69 (t, $J=4.6$ Hz, 4×2H), 2.20 (t, $J=6.8$ Hz, 2×2H), 1.53–1.39 (m, 8H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 151.1, 128.9, 119.5, 85.4, 74.5, 51.9, 48.9, 47.2, 28.5, 28.1, 18.5; MS *m/z* (relative intensity) 322 (M^+-160, 17), 216 (10), 159 (94), 120 (66), 106 (100), 77 (70). Anal. Calcd for $C_{32}H_{42}N_4$: C, 79.62; H, 8.77; N, 11.61. Found: C, 79.60; H, 8.76; N, 11.55.

4.4. Mannich condensation reaction of terminal alkyne with primayl amine and *para*-formaldehyde

(a) 1-Decyne (2.00 mmol), *para*-formaldehyde (6.00 mmol) and benzylamine (2.00 mmol) were mixed well with Al_2O_3 (2.00 g) and cuprous iodide (1.16 g, 6.00 mmol) and placed in the microwave oven and irradiated at 300 W for 10 min, worked up the same as the general procedure. (b) Terminal alkyne (1.00 mmol), *para*-formaldehyde (5.00 mmol) and benzylamine (1.00 mmol) were mixed well with Al_2O_3 (1.00 g) and cuprous iodide (0.58 g, 3.00 mmol) and placed in the microwave oven and irradiated at 30% power for 10 min.

4.4.1. Benzyldi(undec-2-ynyl)amine. Oil; IR (film, $CHCl_3$) 2232 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$) 7.38–7.20 (m, 5H), 3.66 (s, 2H), 3.35 (s, 2×2H), 2.21 (t, $J=6.7$ Hz, 2×2H), 1.55–1.28 (m, 2×12H), 0.88 (t, $J=6.6$ Hz, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.3, 129.3, 128.1, 127.1, 85.3, 75.0, 56.9, 42.3, 31.8, 29.2, 29.1, 28.9, 22.6,

18.7, 14.0; MS *m/z* (relative intensity) 322 (M^+-85, 6), 294 (7), 184 (5), 156 (8), 91 (100). Anal. Calcd for $C_{29}H_{45}N$: C, 85.44; H, 11.13; N, 3.44. Found: C, 85.37; H, 11.24; N, 3.52.

4.4.2. Benzylmethyl(undec-2-ynyl)amine. Oil; IR (film, $CHCl_3$) 2260 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5H), 3.55 (s, 2H), 3.26 (t, $J=2.0$ Hz, 2H), 2.30 (s, 3H), 2.26–2.20 (m, 2H), 1.59–1.28 (m, 12H), 0.88 (t, $J=6.5$ Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.6, 129.2, 128.2, 127.1, 85.8, 74.6, 60.2, 45.5, 41.8, 31.8, 29.2, 29.1, 29.0, 28.9, 22.6, 18.7, 14.0; MS *m/z* (relative intensity) 271 (M^+, 7), 194 (25), 158 (22), 120 (18), 91 (100). Anal. Calcd for $C_{19}H_{29}N$: C, 84.07; H, 10.77; N, 5.16. Found: C, 83.96; H, 10.85; N, 5.19.

4.4.3. Benzylmethyl[3-(phenyl)prop-2-ynyl]amine. Oil; IR (film, $CHCl_3$) 2235 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.48–7.44 (m, 2H), 7.38–7.23 (m, 8H), 3.62 (s, 2H), 3.49 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.3, 131.6, 129.1, 128.1, 127.9, 127.1, 123.2, 85.6, 84.3, 60.1, 45.6, 41.8; MS *m/z* (relative intensity) 235 (M^+, 18), 158 (41), 144 (27), 115 (100), 91 (64). Anal. Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.66; H, 7.43; N, 6.01.

4.4.4. Benzylmethyl[3-(*p*-tolyl)prop-2-ynyl]amine. Oil; IR (film, $CHCl_3$) 2247 cm^{-1} (C≡C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.37–7.24 (m, 7H), 7.09 (d, $J=$ 7.94 Hz, 2H), 3.62 (s, 2H), 3.49 (s, 2H), 2.38 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 138.4, 137.9, 131.5, 129.1, 128.9, 128.2, 127.1, 120.2, 85.7, 83.6, 60.2, 45.7, 41.9, 21.3; MS *m/z* (relative intensity) 249 (M^+, 17), 172 (32), 158 (36), 129 (100), 91 (73). Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.42; H, 7.60; N, 5.57.

4.4.5. Preparation of 4-acetyl-1-ethynylbenzene.[23] To a stirred solution of *p*-bromoacetophone (1.00 g, 5.00 mmol) and Et_3N–dioxane (4 mL/4 mL), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol) and CuI (0.019 g, 0.100 mmol) were added in one portion. Then (trimethylsilyl)acetylene (0.85 mL, 6.00 mmol) was added dropwise at room temperature under nitrogen. The reaction mixture was stirred overnight. Et_3N, dioxane and unreacted (trimethylsilyl)acetylene were removed under reduced pressure. The product extracted with Et_2O (3×20 mL). The combined organic phase was washed with H_2O, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography to generate 0.820 g (85% yield) of 4-acetyl-1-((trimethylsilyl)ethynyl)benzene. Oil; ^1H NMR (250 MHz, $CDCl_3$): δ 7.87 (d, $J=7.9$ Hz, 2H), 7.52 (d, $J=8.4$ Hz, 2H), 2.57 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 196.9, 136.3, 131.9, 128.0, 127.8, 103.9, 97.9, 26.4, -0.29; MS *m/z* (relative intensity) 216 (M^+, 15), 201 (100), 158 (10), 143 (8), 93 (9).

4-Acetyl-1-((trimethylsilyl)ethynyl)benzene (0.648 g, 3.00 mmol) was added to KF/Al_2O_3 (2.00 g, 40% by weight) and stirred at room temperature to ensure efficient mixing. The result mixture was placed in the microwave oven and irradiated at 30% power for 3 min. After cooling, hexane (10 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The product was purified by chromatography to afford 0.415 g (97% yield) of 4-acetyl-1-ethynylbenzene. Mp 68–70 °C (lit.[23] 69–70 °C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.90 (d, $J=8.3$ Hz, 2H), 7.57 (d, $J=8.4$ Hz, 2H), 3.27 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 197.1, 136.7, 132.2, 128.1, 126.8, 82.7, 80.3, 26.5; MS *m/z* (relative intensity) 144 (M^+, 31), 129 (100), 101 (54), 75 (21).

4.4.6. Preparation of 11-dodecyn-2-one.[24] To a suspension of dry pyridinium chlorochromate (4.85 g, 22.5 mmol) in dry CH_2Cl_2 (20 mL), 10-undecyn-1-ol (2.50 g, 15 mmol) and dry CH_2Cl_2 (5 mL) were added dropwise. The reaction mixture was stirred at room temperature for 3 h and the solution was then extracted with ether (3×20 mL). The combined organic layer was dried with Na_2SO_4 and the solvent removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 9:1) to afford 2.00 g (80% yield) of 10-undecyn-1-al.

To a solution of 10-undecyn-1-al (1.50 g, 9.04 mmol) in dry Et_2O (15 mL), CH_3MgBr in ether (3 M, 3.67 mL, 11 mmol) was added at 0 °C over a 1 h period. The reaction mixture was then refluxed for 3 h. Aqueous ammonium chloride was then added to quench the reaction and the mixture was extracted with ether (3×20 mL). The combined organic layer was washed with water and dried with Na_2SO_4 and then the solvent removed under reduced pressure (2 mmHg for 2 h). The crude product was used without purification.

11-Dodecyn-2-ol (crude, 1.4 g) in dry CH_2Cl_2 (5 mL) was added dropwise to a suspension of pyridinium chlorochromate (2.26 g, 10.5 mmol) in dry CH_2Cl_2 (10 mL) dropwise at room temperature. The reaction mixture was stirred at room temperature for 2 days and then extracted with ether (3×20 mL). The combined organic layer was dried with Na_2SO_4 and then the solvent removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate 85:15) to afford 1.20 g (combined yield 74%) of 11-dodecyn-2-one. Oil; ^1H NMR (250 MHz, $CDCl_3$): δ 2.41 (t, $J=7.4$ Hz, 2H), 2.18–2.12 (m, 5H), 1.93 (t, $J=2.4$ Hz, 1H), 1.55–1.28 (m, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 208.5, 84.2, 67.9, 43.4, 29.5, 28.9, 28.8, 28.6, 28.3, 28.1, 23.5, 18.0; MS *m/z* (relative intensity) 165 ($M^+-C_2H_5$, 2), 147 (2), 122 (6), 107 (9), 95 (15), 81 (23), 58 (100).

4.5. Chemoselectivity of Mannich Condensation

(a) *Intermolecular chemoselectivity*. A secondary amine (morpholine or piperazine, 1.00 mmol), terminal alkyne (4-ethynyltoluene or 1-decyne, 1.00 mmol) and an enolizable ketone (acetophone or 2-heptone, 1.00 mmol) were mixed with a mixture of cuprous iodide (0.572 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol) and alumina (1.00 g) in a clean, dry, 10 mL round-bottomed flask at room temperature. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave oven and irradiated at 30% power for 10 min.

(b) *Intramolecular chemoselectivity*. Dibenzylamine or 1-phenylpiperazine (1.00 mmol) and 4-acetyl-1-ethynylbenzene or 11-dodecyn-2-one (1.00 mmol) were added to

a mixture of cuprous iodide (0.572 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol) and alumina (1.00 g) contained in a clean, dry, 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave oven and irradiated at 30% power for 10 min.

4.5.1. [3-(4-Acetylphenyl)prop-2-ynyl]dibenzylamine. Oil; IR (film, $CHCl_3$) 2230 cm^{-1} (C≡C), 1683 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 7.92 (d, $J=8.3$ Hz, 2H), 7.56 (d, $J=8.2$ Hz, 2H), 7.45–7.23 (m, 10H), 3.76 (s, 2×2H), 3.50 (s, 2H), 2.60 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 197.2, 138.7, 136.1, 131.9, 129.0, 128.3, 128.2, 127.2, 88.3, 85.2, 57.8, 42.1, 26.6; MS *m/z* (relative intensity) 194 (M^+-159, 11), 158 (15), 143 (25), 115 (20), 91 (100). Anal. Calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 85.11; H, 6.66; N, 3.94.

4.5.2. 1-Phenyl-4-(tridec-12-oxo-2-ynyl)piperazine. Mp 33–34 °C; IR (film, $CHCl_3$) 2208 cm^{-1} (C≡C), 1711 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$): δ 7.29–7.22 (m, 2H), 6.95–6.82 (m, 3H), 3.31 (s, 2H), 3.23 (t, $J=4.9$ Hz, 2×2H), 2.71 (t, $J=4.9$ Hz, 2×2H), 2.39 (t, $J=7.4$ Hz, 2H), 2.19 (t, $J=6.7$ Hz, 2H), 2.11 (s, 3H), 1.58–1.28 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.2, 151.1, 129.0, 119.6, 116.0, 85.6, 74.5, 51.9, 48.9, 47.3, 43.6, 29.7, 29.2, 29.0, 28.8, 28.7, 28.6, 23.7, 18.6; MS *m/z* (relative intensity) 354 (M^+, 18), 248 (35), 160 (53), 159 (94), 130 (38), 120 (71), 105 (100). Anal. Calcd for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.67; N, 7.90. Found: C, 77.98; H, 9.61; N, 8.02.

4.5.3. Iodination of phenols: preparation of 4-hydroxy-3-iodoacetophenone (representative procedure). 4-Hydroxyacetophenone (1.36 g, 10 mmol) was dissolved in 10 mL of THF–H_2O (50/50, V/V) and I_2 (2.80 g, 11 mmol) and $NaHCO_3$ (0.92 g, 11 mmol) were crushed together and added to the solution. After the mixture was stirred for 3 h at room temperature, residual I_2 was destroyed by addition of a 5% aqueous solution of $Na_2S_2O_3$ until the brown color disappeared. The mixture was extracted with ether (3× 50 mL). The organic phase was dried with Na_2SO_4 and the solvent was removed under pressure. 4-Hydroxy-3-iodoacetophenone (1.23 g, 47% yield) was isolated by column chromatography (silica gel, hexane/ethyl acetate 95:5). Mp 152–154 °C (lit.[25] 153–155 °C); ^1H NMR (250 MHz, CD_3OD): δ 8.29 (s, 1H), 7.82 (d, $J=8.5$ Hz, 1H), 6.86 (d, $J=8.4$ Hz, 1H), 4.91 (s, br, 1H), 2.51 (s, 3H); MS *m/z* (relative intensity) 262 (M^+, 36), 247 (100), 219 (16), 127 (7), 120 (23), 92 (40).

4.5.4. Preparation of *o*-ethynylphenol and *p*-acetyl-*o*-ethynylphenol via a Sonogashira coupling followed by desilylation: synthesis of *o*-ethynylphenol as representative. To a stirred solution of 2-iodophenol (1.10 g, 5.00 mmol) and Et_3N–dioxane (4 mL/4 mL), $PdCl_2(PPh_3)_2$ (0.035 g, 0.05 mmol) and CuI (0.019 g, 0.10 mmol) were added in one portion. Then (trimethylsilyl)acetylene (0.85 mL, 6.00 mmol) was added dropwise at room temperature under nitrogen. The reaction mixture was stirred overnight. Et_3N, dioxane and unreacted (trimethylsilyl)-acetylene were removed under reduced pressure. The product was extracted with Et_2O (3×20 mL) and the combined organic phase washed with H_2O, dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography to afford 0.87 g (86% yield) of *o*-((trimethylsilyl)ethynyl)phenol. Mp 46–48 °C (lit.[26] 46–47 °C); ^1H NMR (250 MHz, $CDCl_3$): δ 7.32 (dd, $J=6.3$ Hz, $J=1.4$ Hz, 1H), 7.20 (dt, $J=7.0$ Hz, $J=1.5$ Hz, 1H), 6.93 (d, $J=8.2$ Hz, 1H), 6.82 (t, $J=7.6$ Hz, 1H), 5.90 (s, 1H), 0.26 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 157.0, 131.6, 130.6, 120.1, 114.5, 109.5, 102.2, 99.0, −0.1; MS *m/z* (relative intensity) 190 (M^+, 18), 175 (100), 159 (19), 135 (13), 115 (16), 77 (14).

o-[(Trimethylsilyl)ethynyl]phenol (0.61 g, 3.00 mmol) was added to KF/Al_2O_3 (2.00 g, 40% by weight) and stirred at room temperature to ensure efficient mixing. The resultant mixture was placed in the microwave oven and irradiated at 30% power for 3 min. After cooling, hexane (10 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The product was purified by chromatography to afford 0.365 g (92% yield) of *o*-ethynylphenol. Oil;[27] ^1H NMR (250 MHz, $CDCl_3$): δ 7.38 (d, $J=7.5$ Hz, 1H), 7.27 (dt, $J=7.7$ Hz, $J=1.0$ Hz, 1H), 6.95 (d, $J=8.2$ Hz, 1H), 6.87 (t, $J=7.5$ Hz, 1H), 5.80 (s, br, 1H), 3.46 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 157.4, 132.0, 130.9, 120.3, 114.8, 108.3, 84.3, 78.3; MS *m/z* (relative intensity) 118 (M^+, 100), 89 (44), 63 (21).

4.5.5. *p*-Acetyl-*o*-[(trimethylsilyl)ethynyl]phenol. Mp 127–129 °C; ^1H NMR (250 MHz, $CDCl_3$): δ 8.00 (d, $J=1.4$ Hz, 1H), 7.87 (d, $J=8.7$ Hz, 1H), 7.00 (d, $J=8.7$ Hz, 1H), 6.63 (s, br, 1H), 2.55 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 196.2, 160.9, 133.0, 131.1, 129.9, 114.8, 109.9, 103.2, 97.8, 26.2, −0.2; MS *m/z* (relative intensity) 232 (M^+, 24), 217 (100), 174 (8), 115 (10), 101 (19). Anal. Calcd for $C_{13}H_{16}O_2Si$: C, 67.20; H, 6.94. Found: C, 67.40; H, 6.84.

4.5.6. *p*-Acetyl-*o*-ethynylphenol. Mp 100–102 °C; ^1H NMR (250 MHz, $CDCl_3$): δ 8.05 (d, $J=1.5$ Hz, 1H), 7.91 (d, $J=8.7$ Hz, 1H), 7.37 (s, 1H), 7.03 (d, $J=8.6$ Hz, 1H), 3.50 (s, 1H), 2.57 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 196.7, 161.6, 133.8, 131.3, 129.6, 115.2, 108.8, 84.4, 77.5, 26.1; MS *m/z* (relative intensity) 160 (M^+, 40), 145 (100), 117 (48), 89 (31). HRMS Calcd for $C_{10}H_8O_2$ 160.0524, found 160.0520.

4.6. One-pot synthesis of 2-substitutited benzo[*b*]furans via the Mannich condensation cyclization sequence reaction of *o*-ethynylphenol with secondary amines and *para*-formaldehyde: general procedure

o-Ethynylphenol (0.18 g, 1.00 mmol) and the secondary amine (1.00 mmol) were added to a mixture of cuprous iodide (0.57 g, 3.00 mmol), *para*-formaldehyde (0.09 g, 3.00 mmol) and alumina (1.00 g) contained in a clean, dry, 10 mL round-bottomed flask. The mixture was stirred at room temperature to ensure efficient mixing. The flask was then fitted with a septum (punctured by an 18 gauge needle), placed in the microwave oven and irradiated at 30% power for 10 min. After cooling, ether (4 mL) was added and the slurry stirred at room temperature to ensure product removal from the surface. The mixture was vacuum filtered using a sintered glass funnel and the product purified by flash

chromatography (hexane/EtOAc as eluting agent) to afford the desired 2-substituted-benzo[*b*]furan.

4.6.1. 1-(Benzofuran-2-ylmethyl)-4-phenylpiperazine. Mp 75–76 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.53–7.46 (m, 2H), 7.26–7.18 (m, 4H), 6.90–6.80 (m, 3H), 6.59 (s, 1H), 3.70 (s, 2H), 3.20 (t, J=4.8 Hz, 2×2H), 2.67 (t, J=4.8 Hz, 2×2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.0, 154.2, 151.1, 129.0, 128.1, 123.9, 122.6, 120.6, 119.6, 116.0, 111.2, 105.7, 55.3, 52.9, 48.9; MS *m/z* (relative intensity) 292 (M^+, 33), 186 (12), 173 (22), 159 (98), 131 (100), 106 (54), 77 (56). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.04; H, 6.89; N, 9.47.

4.6.2. (Benzofuran-2-ylmethyl)dibutylamine.[28] Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50–7.43 (m, 2H), 7.22–7.17 (m, 2H), 6.54 (s, 1H), 3.77 (s, 2H), 2.50 (t, J=7.5 Hz, 2×2H), 1.53–1.46 (m, 2×2H), 1.35–1.27 (m, 2×2H), 0.90 (t, J=7.2 Hz, 2×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 156.2, 154.9, 128.5, 123.5, 122.4, 120.5, 111.1, 104.8, 53.7, 50.7, 29.2, 20.6, 14.0; MS *m/z* (relative intensity) 259 (M^+, 2), 216 (10), 131 (100), 77 (9).

4.6.3. 1-(Benzofuran-2-ylmethyl)piperidine.[29] Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.53–7.45 (m, 2H), 7.27–7.15 (m, 2H), 6.56 (s, 1H), 3.64 (s, 2H), 2.46 (s, br, 2×2H), 1.63–1.57 (m, 2×2H), 1.44–1.42 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.0, 128.3, 123.7, 122.5, 120.5, 111.2, 105.3, 56.1, 54.3, 25.8, 24.1; MS *m/z* (relative intensity) 251 (M^+, 10), 131 (100), 84 (26), 77 (15).

4.6.4. (Benzofuran-2-ylmethyl)benzylmethylamine. Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.52–7.18 (m, 9H), 6.57 (s, 1H), 3.70 (s, 2H), 3.60 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.4, 155.0, 138.4, 129.0, 128.3, 128.2, 127.1, 123.7, 122.5, 120.6, 111.2, 105.2, 61.3, 53.7, 42.1; MS *m/z* (relative intensity) 251 (M^+, 10), 160 (13), 131 (100), 91 (27), 77 (13). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.25; H, 6.82; N, 5.56.

4.6.5. 4-(Benzofuran-2-ylmethyl)morpholine. Mp 50–51 °C (lit.[30] 51–52 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.54–7.46 (m, 2H), 7.28–7.17 (m, 2H), 6.60 (s, 1H), 3.74 (t, J=4.6 Hz, 2×2H), 3.67 (s, 2H), 2.54 (t, J=4.5 Hz, 2×2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.1, 154.0, 128.1, 123.9, 122.6, 120.6, 111.2, 105.8, 66.7, 55.8, 53.4; MS *m/z* (relative intensity) 217 (M^+, 14), 144 (9), 131 (100), 86 (26), 77 (17).

4.6.6. (Benzofuran-2-ylmethyl)methyl(1-naphthalenemethyl)amine. Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.20–8.17 (m, 1H), 7.80–7.70 (m, 2H), 7.50–7.32 (m, 6H), 7.26–7.14 (m, 2H), 6.57 (s, 1H), 3.94 (s, 2H), 3.76 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.5, 155.0, 134.3, 133.8, 132.4, 128.3, 128.0, 127.4, 125.9, 125.5, 125.0, 124.5, 123.8, 122.5, 120.6, 111.1, 105.4, 59.4, 54.2, 42.3; MS *m/z* (relative intensity) 301 (M^+, 9), 207 (8), 160 (42), 141 (61), 131 (100), 115 (19), 77 (13). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.71; H, 6.53; N, 4.68.

4.6.7. 2-(Benzofuran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline. Mp 58–59 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.53–7.45 (m, 2H), 7.25–6.95 (m, 6H), 6.62 (s, 1H), 3.83 (s, 2H), 3.71 (s, 2H), 2.90 (t, J=5.3 Hz, 2H), 2.82 (t, J=5.4 Hz, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.0, 154.6, 134.3, 133.9, 128.5, 128.2, 126.5, 126.1, 125.5, 123.8, 122.5, 120.6, 111.2, 105.4, 55.6, 54.9, 50.5, 28.8; MS *m/z* (relative intensity) 263 (M^+, 5), 145 (19), 131 (100), 104 (23), 77 (21). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.96; H, 6.57; N, 5.30.

4.6.8. (Benzofuran-2-ylmethyl)di(isopropyl)amine. Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.50–7.41 (m, 2H), 7.20–7.16 (m, 2H), 6.57 (s, 1H), 3.77 (d, J=0.59 Hz, 2H), 3.18–3.08 (m, 2H), 1.06 (d, J=6.6 Hz, 4×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 160.2, 154.8, 128.9, 123.0, 122.3, 120.3, 110.9, 103.2, 49.0, 42.9, 20.7; MS *m/z* (relative intensity) 231 (M^+, 3), 216 (9), 131 (100). Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.16; H, 9.36; N, 5.97.

4.6.9. 1-(Benzofuran-2-ylmethyl)-2,2,6,6-tetramethylpiperidine. Mp 88–89 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48–7.36 (m, 2H), 7.17–7.14 (m, 2H), 6.63 (s, 1H), 3.81 (s, 2H), 1.60–1.51 (m, 6H), 1.06 (s, 4×3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.5, 154.5, 129.1, 122.7, 122.2, 120.2, 110.7, 102.9, 54.9, 42.4, 41.2, 27.4, 17.8; MS *m/z* (relative intensity) 271 (M^+, 2), 256 (15), 131 (100), 77 (7). Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.28; N, 5.16. Found: C, 79.40; H, 9.36; N, 4.91.

4.6.10. (Benzofuran-2-ylmethyl)methylaniline. Oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.48–7.41 (m, 2H), 7.28–7.15 (m, 4H), 6.86–6.72 (m, 3H), 6.49 (s, 1H), 4.61 (s, 2H), 3.08 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.2, 154.9, 149.1, 129.2, 128.4, 123.7, 122.6, 120.6, 117.3, 112.9, 111.0, 103.9, 50.5, 38.6; MS *m/z* (relative intensity) 237 (M^+, 13), 207 (26), 131 (100), 96 (9), 77 (23). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.17; H, 6.61; N, 5.63.

4.6.11. 1-(5-Acetylbenzofuran-2-ylmethyl)-4-phenylpiperazine. Mp 111–113 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.93 (d, J=8.6 Hz, 1H), 7.52 (d, J=8.7 Hz, 1H), 7.25 (t, J=7.7 Hz, 2H), 6.93–6.82 (m, 3H), 6.17 (s, 1H), 3.76 (s, 2H), 3.24 (t, J=4.7 Hz, 2×2H), 2.72 (t, J=4.7 Hz, 2×2H), 2.65 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 197.5, 157.6, 156.1, 151.1, 132.6, 129.0, 128.3, 124.7, 122.0, 119.7, 116.1, 111.2, 106.2, 55.3, 53.0, 49.0, 26.7; MS *m/z* (relative intensity) 334 (M^+, 25), 228 (11), 201 (55), 173 (64), 130 (36), 106 (87), 56 (100). HRMS Calcd for $C_{21}H_{22}N_2O_2$ 334.1681, found 334.1690.

4.6.12. 1,4-Bis(benzofuran-2-ylmethyl)piperazine. Mp 143–144 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.52–7.44 (m, 4H), 7.29–7.15 (m, 4H), 6.58 (s, 2×1H), 3.69 (s, 2×2H), 2.62 (s, br, 4×2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 155.0, 154.3, 128.2, 123.8, 122.6, 120.6, 111.2, 105.6, 55.3, 52.7; MS *m/z* (relative intensity) 346 (M^+, 2), 215 (46), 131 (100), 77 (15). Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.05; H, 6.51; N, 7.99.

4.7. General procedure for recycling

After carried out a Mannich condensation, ether was added to remove the product from the cuprous iodide and alumina

surface. After filtration, the Cu/Al_2O_3 was directly used for the next trial.

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