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Efficient construction of a β-naphthol library under continuous flow conditions†

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A β-naphthol library has been efficiently constructed utilizing a mild continuous flow procedure, relying on a tandem Friedel–Crafts reaction and starting from readily available arylacetyl chloride and alkynes. Multiple functionalized β-naphthols can be acquired within 160 s in generally high yields (up to 83%). Using an electron-rich phenylacetyl chloride derivative (4-OH- or 4-MeO-) provides spirofused triene dione as the primary product. A scale-up preparation affords a throughput of 4.70 g h^{-1}, indicating potential large-scale application. Herein, we present a rapid, reliable, and scalable method to obtain various β-naphthols in the compound library.

Introduction

β-Naphthols are essential structural elements ubiquitous in a diverse range of natural products[1] and pharmaceutical agents[2] (Fig. 1). Furthermore, they serve as the critical synthetic precursor for the preparation of chiral binaphthyl compounds, especially BINOL,[3] BINAP,[4] and BNDHP,[5] which play a significant role in asymmetric synthesis. β-Naphthols are also versatile synthetic intermediates that can be transformed into valuable molecules.[6] Due to their wide application in pharmaceutical and agrochemical fields, investigating methodologies for the efficient synthesis of β-naphthols has attracted intensive interest in organic chemistry.

Over the past few decades, several synthetic methods have been developed for the construction of mono- or poly-substituted β-naphthols, generally relying on intramolecular cyclization reactions such as electrocyclization,[7] Dieckmann[8] and Aldol[9] condensation, Pd-catalyzed annulation,[10] oxidative cyclization.[11] However, the known synthetic strategies typically suffer from some drawbacks, such as long synthetic sequences, modest regioselectivity, limited substrate scope, and not readily available starting materials. It is worth noting that the tandem Friedel–Crafts reaction of easily available arylacetyl chloride with alkynes provided selectively 3,4-disubstituted β-naphthols, affording a unique strategy for obtaining β-naphthols (Scheme 1).[12]

As an emerging and prospective technique, continuous flow considerably improves chemical synthesis productivity[13] and provides a powerful tool to address long-standing challenges in academia and industry.[14] The flow process is enabled by utilizing the micro-reactor, which has a high surface/volume ratio that permits rapid heat and mass transfer.[15] Furthermore, the precise control of reaction parameters (time, temperature, and mixing) in continuous flow gives fast condition screening and efficient synthesis, and a reliable and straightforward scale-up was also readily achieved by raising the flow rate, processing time, or micro-reactor volume.[16] It was found that Friedel–Crafts reaction was particularly suitable to conduct under continuous flow conditions and typically showcased improved performance than the batch process.[17] Out of

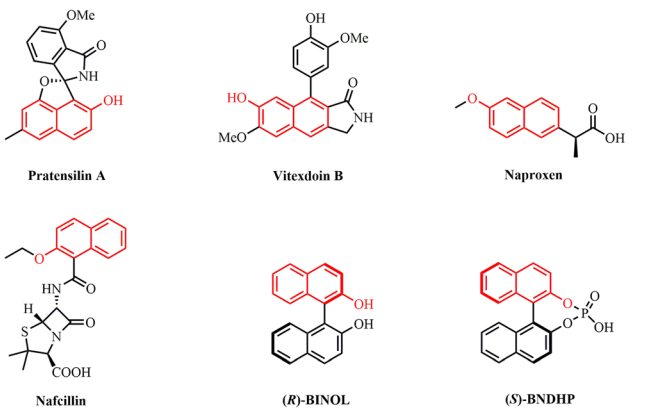
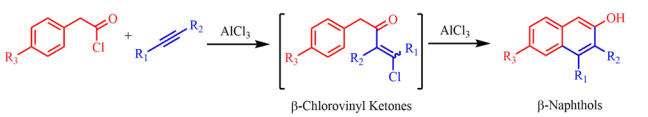


Fig. 1 Bioactive and functional compounds containing β-naphthol moieties.



Scheme 1 The synthesis of β-naphthols from arylacetyl chloride with alkynes.

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our keen interest in asymmetric catalysis, various β-naphthols were in demand as building blocks to prepare chiral binaphthyl ligands. Herein, we disclose an efficient continuous flow procedure to rapidly establish a β-naphthol library that relies on tandem Friedel–Crafts reaction starting from arylacetyl chloride and alkynes, to satisfy the demand for multiple β-naphthols.

Results and discussion

In preliminary experiments, our investigation focused on the reaction between phenylacetyl chloride (**1a**) and diphenylacetylene (**2a**) in a simple continuous flow system, which comprised two HPLC pumps, a T-shaped mixer (Mixer, PEEK, 1/16″ I.D.), and a coil reactor (Reactor, PFA, 1/16″ O.D., 5.9 mL internal volume). As shown in Fig. 2, **1a** and $AlCl_3$ were mixed in CH_2Cl_2 and sonicated for 1 min to provide a clear complex solution. **1a**-$AlCl_3$ solution (0.1 M in CH_2Cl_2) was driven by an HPLC pump at a given flow rate (A mL min^{-1}) into Mixer, where it was mixed with **2a** solution (0.1 M in CH_2Cl_2) and delivered by the other HPLC pump at a flow rate of B mL min^{-1}. The reaction was performed as the combined stream was passed through Reactor with a residence time of t_R s. After quenching with H_2O and the usual workup, the target product β-naphthol **3a** was obtained.

Various reaction parameters (reagent dosage, residence time, temperature, and concentration) were screened; the results were summarized in Table 1. Considering the critical role of $AlCl_3$ in the Friedel–Crafts reaction, the amount of $AlCl_3$ was first investigated. Keeping the flow rate of two solutions at 1.0 mL min^{-1}, using 1.1 equiv. of $AlCl_3$, and with a residence time of 176 s, the β-Naphthol **3a** was only obtained in a low yield of 49% (entry 1). The elevated $AlCl_3$ to 1.3 equiv. resulted in an increased formation of **3a** and still with a surplus of **2a**, while the higher amount (1.5 equiv.) provided similar results (entries 2 and 3). Thus, the use of 1.3 equiv. of $AlCl_3$ was most advantageous. Our further attempts to improve the yield focus on enhancing the amount of **1a**-$AlCl_3$. After increasing the flow rate of **1a**-$AlCl_3$ solution from 1.1 to 1.5 mL min^{-1}, the best result (83% yield) was achieved at a flow rate of 1.2 mL min^{-1} and with a residence time of 160 s (entry 5). It had a detrimental impact on the formation of **3a** when the flow rate elevated further, probably due to reduced reaction time (entries 6 and 7). In addition, there was no measurable yield improvement on extending the reaction time to 320 s by lowering the flow rate

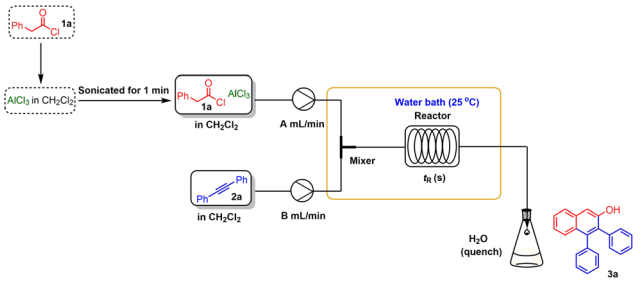

Fig. 2 The flow system for the synthesis of β-naphthol **3a**.

Table 1 Condition screen results of the reaction between phenylacetyl chloride and diphenylacetylene

Entry	*A* (mL min^{-1})	*B* (mL min^{-1})	$AlCl_3$[a] (equiv.)	t_R (s)	Yield[b] (%)
1	1.0	1.0	1.1	176	49
2	1.0	1.0	1.3	176	63
3	1.0	1.0	1.5	176	65
4	1.1	1.0	1.3	168	78
5	1.2	1.0	1.3	160	83
6	1.3	1.0	1.3	153	79
7	1.5	1.0	1.3	141	72
8	0.6	0.5	1.3	320	84
9	1.8	1.5	1.3	107	64
10	2.4	2.0	1.3	80	60
11[c]	1.2	1.0	1.3	160	56
12[d]	1.2	1.0	1.3	160	81
13[e]	1.2	1.0	1.3	160	66
14[f]	1.2	1.0	1.3	160	80
15[g]	1.2	1.0	1.3	160	Trace

[a] Relative to phenylacetyl chloride. [b] Isolated yield based on the starting diphenylacetylene. [c] The coil reactor was dipped in a cooling bath at 0 °C. [d] The coil reactor was dipped in a water bath at 40 °C. [e] The concentration of **1a** and **2a** in CH_2Cl_2 were 0.05 M. [f] The concentration of **1a** and **2a** in CH_2Cl_2 were 0.2 M. [g] $BF_3 \cdot Et_2O$ was used in this case.

(entry 8), and decreased yields were observed when shortening the residence time to 107 s and 80 s (entries 9 and 10). The influence of temperature was also examined; performing the reaction at 0 °C led to a lower yield of **3a** (entry 11), but increasing the reaction to 40 °C could be well tolerated (entry 12). Furthermore, the screen results for the concentration revealed that the low concentration at 0.05 M was detrimental to the generation of **3a** (entry 13); however, the higher concentration (0.2 M) gave a satisfactory outcome (entry 14). We also evaluated $BF_3 \cdot Et_2O$ as the Lewis acid instead of $AlCl_3$, but only trace amounts of the desired product were obtained.

Thus, the optimized flow conditions for the preparation of β-naphthol were obtained as follows. A solution of **1a**-$AlCl_3$ (0.1 M in CH_2Cl_2, 1.3 equiv. $AlCl_3$ relative to **1a**, 1.2 mL min^{-1}) and a solution of **2a** (0.1 M in CH_2Cl_2, 1.0 mL min^{-1}) were introduced to Mixer with HPLC pumps. The combined stream was passed through Reactor with a residence time of 160 s at 25 °C, furnishing β-naphthol **3a** with 83% yield after quenching with H_2O.

With the efficient continuous flow protocol, we next explored the rapid development of a β-naphthol library under continuous flow conditions. Firstly, the substrate scope for phenylacetyl chloride with various alkynes was evaluated in the flow system (Table 2). The alkyl disubstituted internal alkyne (**2b**) could be smoothly converted into 3,4-disubstituted β-naphthol with moderate yield (entry 1, 70%). While the asymmetric disubstituted alkyne (**2c**) with aryl and alkyl substituents led to the regioselective generation of 3,4-disubstituted product, providing a high yield of β-naphthol (entry 2, 81%). The terminal alkynes bearing aryl or alkyl substituents (**2d–2g**) were also well-tolerated, affording the 4-substituted β-naphthol with good yields ranging from 74 to 78% (entries 3–6). Interestingly,

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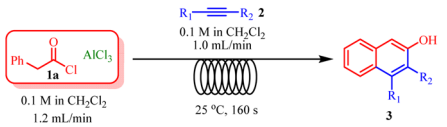
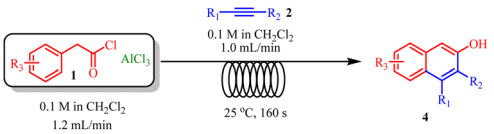
Table 2 Reaction of phenylacetyl chloride with various alkynes under continuous flow conditions



Entry	Alkyne	Product	Yield[a] (%)
1	2b	3b	70
2	2c	3c	81
3	2d	3d	74
4	2e	3e	77
5	2f	3f	75
6	2g	3g	78
7	2h	3h	82
8	2i	3i	53
9	2j	3j	39

[a] Isolated yield based on the starting alkyne.

Table 3 Reaction of various arylacetyl chlorides with alkynes under continuous flow conditions



Entry	Acyl chloride	Alkyne	Product	Yield[a] (%)
1	1b	2a	4a	73
2	1b	2g	4b	68
3	1c	2g	4c	74
4	1d	2g	4d	78
5	1e	2a	4e	65
6	1e	2g	4f	55
7	1f	2a	4g : 4e	21 : 63
8	1f	2g	4h : 4f	12 : 75
9	1g	2a	4i	72
10	1g	2d	4j	64
11	1g	2g	4k	69
12	1h	2a	4l	58
13	1h	2g	4m	51
14	1i	2a	4n	44
15	1i	2g	4o	37
16				91

subjecting trimethylsilylacetylene (**2h**) to the flow system, 2-naphthol (**3h**) could be selectively obtained in superior yield (82%) and with the removal of the TMS group (entry 7); the result was different from the mixture obtained in batch previously reported in the literature.[12] Furthermore, the presence of electron-withdrawing functional group (Cl, OAc) in the alkyl terminal alkynes (**2i** and **2j**) was also compatible furnished the corresponding products with lower yields (entries 8 and 9); these groups could be used for further functionalization.

In order to enlarge the substrate scope in the β-naphthol library, the flow synthesis was carried out by modifying the arylacetyl chlorides and alkynes (Table 3). 4-Methylphenylacetyl chloride (**1b**) was examined in the reaction of diphenylacetylene and 1-decyne, provided the β-naphthols in moderate yields (entries 1 and 2, 73% and 68%). The 2-methylphenylacetyl chloride (**1c**) and 4-*tert*-butyl phenylacetyl chloride (**1d**) were also well-tolerated in the reaction of 1-decyne; the corresponding products were obtained with good

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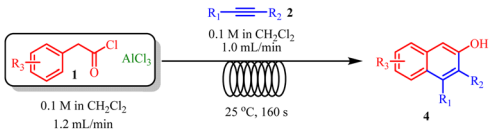
Table 3 (*Contd.*)

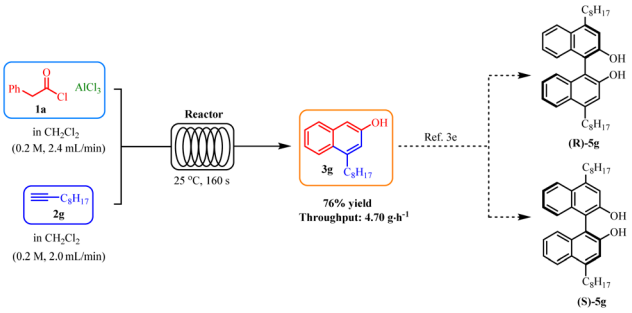


Entry	Acyl chloride	Alkyne	Product	Yield[a] (%)

[a] Isolated yield based on the starting alkyne.

yields (entries 3 and 4, 74% and 78%). Interestingly, the reaction of electron-rich 4-hydroxyphenylacetyl chloride (**1e**) with diphenylacetylene and 1-decyne both resulted in the formation of spiro adducts instead of β-naphthol (entries 5 and 6). Similarly, 4-methoxyphenylacetyl chloride (**1f**) was reacted with diphenylacetylene and 1-decyne, affording spirofused triene dione (**4e** and **4f**) as the primary product (63% and 75%); however, a small amount of β-naphthol (**4g** and **4h**) were still generated (entries 7 and 8). In addition, 3-methoxyphenylacetyl chloride (**1g**) was smoothly transformed into β-naphthols through the reaction with diphenylacetylene, phenylacetylene, and 1-decyne; the yields ranged from 64–72% (entries 9–11). The evaluation of the electron-deficient phenylacetyl chloride derivative demonstrated that it has lower reactivity; the reaction of 4-chlorophenylacetyl chloride (**1h**) with diphenylacetylene and 1-decyne led to moderate yields of products (entries 12 and 13) while worse results were observed with 3,4-dichlorophenylacetyl chloride (**1i**), furnished the desired products in poor yields (entries 14 and 15). Finally, using 1-naphthalacetyl chloride (**1j**) resulted in the formation of cyclobutanaphthalenone with 91% yield (entry 16), which was presumably due to poor electrophilicity of **1j**, the β-chlorovinyl ketone intermediate could not be obtained, the own Friedel–Crafts acylation reaction was performed instead.

To evaluate the scalability of the continuous flow procedure we developed in the synthesis of β-naphthol, a scale-up preparation of **3g** was performed in a coil reactor with an enlarged internal volume of 11.8 mL (Scheme 2). Thus, utilizing **1a**-$AlCl_3$ (0.2 M in CH_2Cl_2, 1.3 equiv. $AlCl_3$ relative to **1a**, 2.4 mL min^{-1}) and **2g** (0.2 M in CH_2Cl_2, 2.0 mL min^{-1}), with a residence time of 160 s at 25 °C, 7.05 g of 4-octylnaphthalen-2-ol (**3g**, 76% yield) was straightforwardly produced after 1.5 h processing time, corresponding to a throughput of 4.70 g h^{-1}. The yield was similar to the previous small reaction, suggesting that the reaction conditions used to synthesize small-scale products could be transferred to a larger scale without further optimization. Additionally, the synthetically important chiral BINOL derivatives could be obtained using the method reported in the literature.[3e]



Scheme 2 Scale-up preparation of β-naphthol under continuous flow conditions and the synthesis approach to BINOL derivatives.

Conclusions

In summary, a β-naphthol library has been prepared through a continuous flow protocol based on tandem Friedel–Crafts reaction and using readily available arylacetyl chloride and alkynes. A broad range of functionalized β-naphthols could be obtained within 160 s in generally high yields (up to 83%). Interestingly, using electron-rich (4-OH- or 4-MeO-) substituted phenylacetyl chloride afforded spirofused triene dione as the primary product. Furthermore, a scale-up preparation of **3g** proceeded stably with a throughput of 4.70 g h^{-1}, demonstrating reliable and efficient scale-up performance. Featuring mild reaction conditions, short reaction time, and broad substrate scope, the flow procedure furnished a rapid and scalable approach to acquire β-naphthols, the essential synthetic precursor preparing chiral binaphthyl ligands. The following work about asymmetric catalysis will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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