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Synthesis of polysubstituted-2-naphthols

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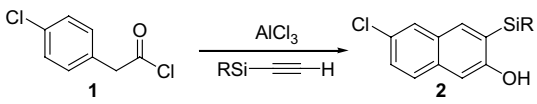
Abstract—Substituted 3-(triisopropylsilyl)-2-naphthols are prepared by an aluminum chloride catalyzed condensation of phenyl acetyl chloride derivatives and triisopropylsilyl acetylene. The yields obtained are in the range of 41% to 67%. The reaction is regiospecific and gives only the 3-(trialkylsilyl)-2-naphthol isomer.

Naphthol derivatives are important molecules found in many drugs such as naproxen, nabumetone, and nafamostat.[1] Our interest in substituted naphthols laid in the ability of the hydroxyl group to be converted to a triflate derivative, which is known to couple with aryl halides.[2] We used the 2-naphthol moiety as a building block in the synthesis of some highly potent EP_3 antagonists,[2] and in order to improve the metabolism profile and to establish a SAR with the naphthyl group, we required an easy and versatile synthesis of substituted 2-naphthols. Herein we wish to describe a new and regiospecific procedure for the preparation of polysubstituted 2-naphthols via an aluminum chloride catalyzed condensation of phenylacetyl chloride derivatives and trialkylsilyl acetylenes.

Our first successful reaction was carried out at −20 °C with 4-chlorophenylacetyl chloride and trimethylsilyl acetylene producing 6-chloro-3-(trimethylsilyl)-2-naphthol in 42% yield (Table 1, entry 1). Since all attempts to increase the yield by varying conditions such as temperature and Lewis acid failed, we turned our attention on increasing the substitution on the silicon group to increase the stability of the silyl acetylenes toward decomposition. Therefore, a series of mono substituted silyl acetylenes were submitted to the previous reaction conditions, and the results are summarized in Table 1.

Changing the substitution on the alkyne from trimethylsilyl to triethylsilyl increased the yield to 53% (entry 2). We could further improve the yield with either *tert*-butyldimethylsilyl (entry 3, 60% yield) or with triisopropylsilyl acetylene (entry 4, 62% yield) but no reaction was observed with dimethylphenyl and triphenylsilyl acetylene (entries 5 and 6).

Table 1. Synthesis of 3-trialkylsilyl-6-chloro-2-naphthol



1 2

Entry	R	Yield (%)
1	$(CH_3)_3$	42
2	$(CH_3CH_2)_3$	53
3	*t*-Bu$(CH_3)_2$	60
4	$((CH_3)_2CH)_3$	62
5	Ph$(CH_3)_2$	0
6	Ph_3	0

Various acid chlorides were then prepared and reacted with triisopropylsilylacetylene and these results are summarized in Table 2.[3]

In general, every substitution studied gave satisfactory yields. Substitution at the 4-position of the ring is well tolerated (Table 2, entries 3, 4, 5, and 6, with 58–63% yield) while substitution at the 2-position gave a lower yield as shown with example 2 (41% yield). Interestingly, reactant bearing an electron-donating group such as a methoxy group gave a lower yield of the desired naphthol (entry 7, 12% yield). The reaction was not very efficient due to the formation of a spiro adduct[4] as described by Haack et al.[5,6] The 3,5-disubstitution on the phenyl ring afforded the 5,7-dimethyl-3-(triisopropylsilyl)-2-naphthol in 50% yield (entry 8). The acetylene

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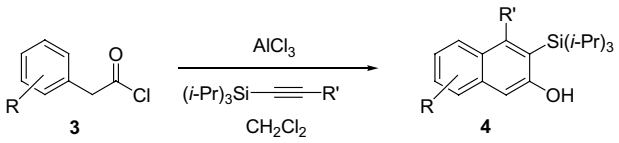
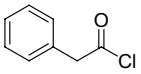
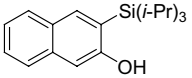
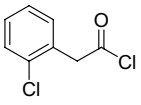
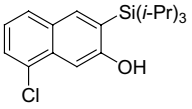
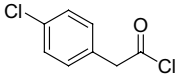
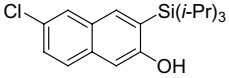
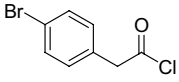
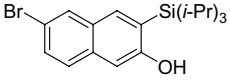
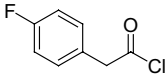
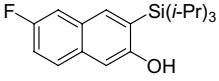
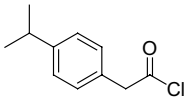
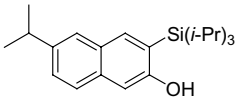
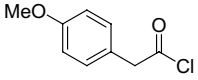
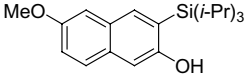
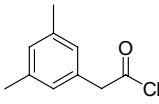
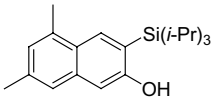
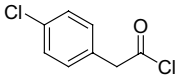
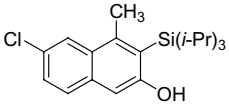
Table 2. Synthesis of substituted 3-(triisopropylsilyl)-2-naphthol[9,10]

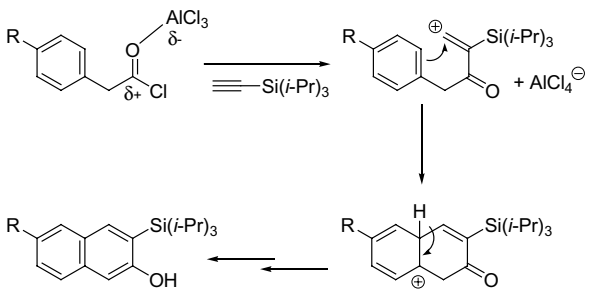


Entry	Substrate	R′	Product	Yield (%)
1		H		67
2		H		41
3		H		62
4		H		58
5		H		62
6		H		63
7		H		12
8		H		50
9		CH_3		67

used could also be disubstituted to obtain more complex molecules. This is illustrated with triisopropylsilyl propyne (entry 9) where under the same conditions, we obtained 67% of the trisubstituted naphthol.

One important feature of this reaction is the regiospecificity. The only regioisomer formed is the 3-(trialkylsilyl)-2-naphthol (determined by NOE). We hypothesize that the reaction proceeds first by addition of the alkyne onto the acid chloride via the most hindered carbon. This result may be rationalized in terms of the greater stability of the vinylic cation when substituted with a silicon group at the β-position, which leads to only one isomer upon ring closure (Scheme 1).[7]

In conclusion, we have developed a new and regiospecific one-step procedure for the preparation of substituted 2-naphthol derivatives via the reaction of substituted phenylacetyl chlorides, triisopropylsilyl acetylene, and aluminum chloride. These polysubstituted naphthols, bearing a silyl group, can be further functionalized to halides, alkyl or aromatic groups.[8]



Scheme 1.

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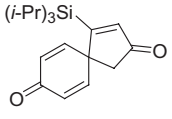
3. The acid chlorides were prepared by treatment of the corresponding acid with oxalyl chloride and a catalytic amount of DMF.
4. The spiro adduct was isolated in 24% yield and the structure assigned as compound **5**.



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9. Typical procedure for the preparation of 6-chloro-3-(triisopropylsilyl)-2-naphthol. To a solution of aluminum chloride (706 mg, 5.3 mmol) in 3.8 mL of CH_2Cl_2 at −20 °C was slowly added a solution of 4-chlorophenylacetyl chloride (500 mg, 2.65 mmol) in 1.3 mL of CH_2Cl_2. The triisopropylsilyl acetylene (2.1 ml, 9.26 mmol) was then slowly added and the mixture stirred at −20 °C for 30 min. The reaction mixture was poured into ice, a solution of Rochelle' salt (2 M) was added, and the mixture stirred for 30 min. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ satd soln, brine, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate; 90/10) to give the 6-chloro-3-(triisopropylsilyl)-2-naphthol (530 mg, 60% yield). Mp: 63–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.82 (d, J = 1.7 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.39 (dd, J = 2.0, 8.7 Hz, 1H), 7.0 (s, 1H), 5.05 (br s, 1H), 1.64 (m, 3H), 1.18 (d, J = 7.5 Hz, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.2, 137.4, 133.2, 129.1, 128.6, 127.4, 127.0, 126.6, 125.8, 108.2, 18.8, 11.6. Elemental analysis calcd for $C_{19}H_{27}ClOSi$: C, 68.13; H, 8.12; found: C, 67.92; H, 8.50.
10. All compounds gave satisfactory elemental analysis or high resolution mass spectrometry.