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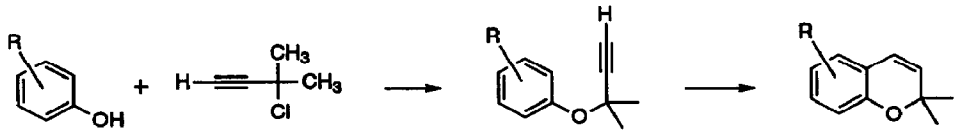
Improved Synthesis of Aryl 1,1-Dimethylpropargyl Ethers

**Jollie D. Godfrey, Jr.,* Richard H. Mueller, Thomas C. Sedergran,†
Nachimuthu Soundararajan,† and Vincent J. Colandrea†**

Chemical Process Research, Bristol-Myers Squibb, P.O. Box 4000, Princeton, NJ 08543-4000
†Chemical Process Technology, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, NJ 08903

Abstract: An efficient, general, and practical synthesis of aryl 1,1-dimethylpropargyl ethers has been developed.

A large number of natural 2,2-dimethylchromene (2,2-dimethyl-2*H*-1-benzopyran) derivatives **3** are known and have been the subject of considerable interest due to their biological activity in plants and animals.[1] Recently, several pharmacologically active compounds[2] have generated intense interest in the synthesis of 2,2-dimethylchromenes, particularly those bearing an electron withdrawing group. The O-alkylation of phenols with 3-chloro-3-methylbutyne **1** followed by thermal rearrangement of the resulting aryl 1,1-dimethylpropargyl ether **2** remains a convenient method for the preparation of 2,2-dimethylchromenes **3**.[3] This method is based on the work of Iwai and Ide[4] who demonstrated that thermal rearrangement of simple aryl propargyl ethers yielded chromenes. Over the last 25 years a variety of conditions have been used for the alkylation of phenols with **1**; the most popular method involves the use of K_2CO_3 and KI in refluxing acetone, often with **1** in considerable excess. Similar alkylation of phenols bearing an electron withdrawing substituent (*e.g.*, 4-CN, 4-NO_2, 4-CH_3CO) is often best performed using a phase transfer[5] method; however, a long reaction time (4 days) is required.

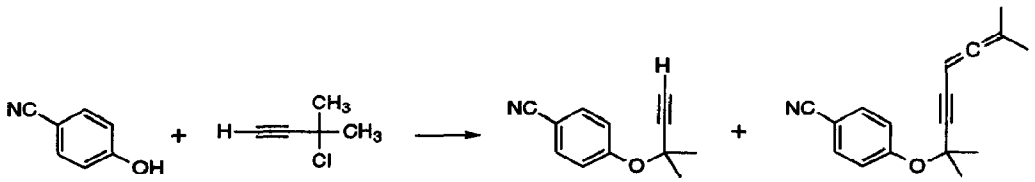


1 **2** **3**

An ongoing project required the preparation of a substantial amount of **4**.[6] Treatment of 4-cyanophenol with **1** (1.5 eq) in refluxing 2% aqueous acetone (bp 56°C) containing K_2CO_3/KI gave a conversion too slow to be of any practical value. Replacement of acetone with higher boiling 2-butanone (bp 80°C) resulted in complete conversion to **4** in 13 hours; however, this heterogeneous reaction proved unreliable on scale up.

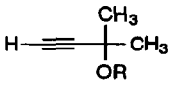
Our focus was then directed toward the development of a homogeneous reaction suitable for the preparation of **4**. Much to our delight, a nearly quantitative yield of **4** was obtained by treatment of 4-cyanophenol with **1** (1.5 eq) in CH_3CN containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.1 eq) at room temperature for 21 hours. Upon further investigation this reaction also proved capricious as the reaction rate and conversion varied greatly. Eventually this variability was correlated to the use of an old or a new syringe needle for reagent transfer. Older needles tended to give better reactions than new needles. We reasoned that some catalytically active species was being introduced with older needles. Syringe needles consist of the

needle itself and a hub; the needle typically is stainless steel, the hub typically nickel-plated brass, an alloy of copper and zinc. After frequent use with corrosive materials, the brass often becomes exposed, and a trace amount of a metal could be transferred to the reaction mixture via the use of an older needle. In the event, treatment of 4-cyanophenol with **1** (1.1 eq) in CH_3CN containing DBU (1.3 eq) and CuCl (0.003 eq, 0.3 mole%) resulted in ~90% conversion in 2.5 hours at 0°C![7] In addition, the reaction now proved consistent and reproducible. A side product, allenyne **5** (~5%), also was generated by further reaction of **4**. The formation of **5** was minimized (~1%) by use of less CuCl (0.02 mole%, 10 hours at 0°C) and **1** (0.9 eq) as the limiting reagent. Under these mild conditions excellent (and consistent) yields (81% based on **1**) of **4** can be obtained. A subsequent literature survey has revealed reports of CuCl catalyzed alkylation of carbon[8] and nitrogen[9] centers with **1**. Quite surprisingly, Cu(I) catalysis appears not to have been previously applied to a similar alkylation of phenols. We have now shown that Cu(II) salts are also effective catalysts for this reaction. We suggest that an Eglinton/Glaser[10] type oxidative coupling of terminal alkynes occurs with the formation of a diyne and the *in situ* generation of the catalytically active Cu(I) species.



1 **4** **5**

The preparation of **1**[11] is, at best, environmentally unfriendly (large waste stream) and exposure to the volatile **1** (bp 76°C) may represent a potential hazard. We therefore turned our attention to the development of an alternative to **1**. The self condensation of acetate **7**[12] or methyl carbamate **8**,[13] under the influence of an amine and CuCl, to yield an allenyne suggested that a derivative of 2-methyl-3-butyn-2-ol **6** could be a useful alternative to **1**. Treatment of 4-cyanophenol with carbonate **9**[14] in CH_3CN containing DBU and $CuCl_2$ (0.3 mole%) at 0°C for 24 hours gave **4** in an excellent yield (86% based on 4-cyanophenol).[7] The reduced reactivity of **9**, in comparison to **1**, required an increased amount of catalyst and longer reaction time; however, **9** can be used in slight excess (1.1 eq) without forming an excessive amount of allenyne **5**. Carbonate **9** was prepared by treatment of **6** with *n*-butyl lithium followed by methyl chloroformate and was impractical for large scale work; therefore, we continued our search for an alternative to **1**.

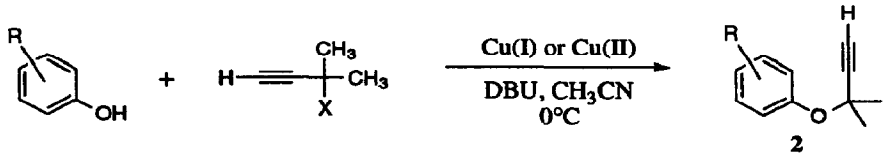


6 R = H
7 R = $COCH_3$
8 R = $CONHCH_3$
9 R = CO_2CH_3
10 R = COPh
11 R = $COCF_3$

With 4-cyanophenol, acetate **7** proved too unreactive to be of practical value and benzoate **10**[15] gave ~55% conversion to **4** after 15 hours at 0°C using CuCl (2 mole%) as catalyst. This result suggested that an ester of **6** using a stronger acid may be useful and this expectation was realized with trifluoroacetate **11**. Treatment of **6** with trifluoroacetic anhydride in CH_3CN containing DBU at 0°C gave the desired trifluoroacetate **11** which proved unstable to an aqueous workup. However, without isolation, addition of **11** to a solution of 4-cyanophenol in CH_3CN containing $CuCl_2$ (0.1 mole%) and DBU at 0°C afforded **4** in excellent yield (86% based on 4-cyanophenol).

The conversion of a variety of phenols to the corresponding propargyl ethers using **1**, **9**, and **11** with copper catalysis is shown below; good to excellent yields (non-optimized) were obtained in all cases. The crude propargyl ethers thus prepared are suitable, as judged by NMR and chromatographic analysis, for direct conversion to the corresponding 2,2-dimethylchromenes. This copper-catalyzed process works well with phenols bearing electron-withdrawing or donating groups; however, phenols capable of chelation with copper (*e.g.*, salicylaldehyde) may require an increased amount of catalyst to obtain a reasonable reaction rate.

Thus, an efficient, general, and practical method for the preparation of aryl 1,1-dimethylpropargyl ethers under extremely mild conditions has been developed. The preparation and *in situ* use of trifluoroacetate **11** allows for a one-step preparation of aryl 1,1-dimethylpropargyl ethers and should find widespread use. This methodology should also be applicable to the synthesis of other aryl 1,1-disubstituted propargyl ethers.



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R	**1** (X = Cl) yield (%)[a]	**9** (X = OCO_2CH_3) yield (%)[b]	**11** (X = $OCOCF_3$) yield (%)[b]	**2** (lit. ref.)
4-CN	78	86	86	6
4-NO_2	81	78	88	6
2-CHO	74[c]	85[d]	50	16
4-$COCH_3$	78	86	80	17
4-OCH_3	67	70	63	3
3-NO_2	80	85	76	18
4-I	79	86	78	19
H	69	70	83	3
3-CF_3	74	79	72	20
4-$NHCOCH_3$	81 (crude)	77 (crude)	61 (crude)	6
	63[e]	68[e]		

Yields refer to purified (bulb to bulb distilled at reduced pressure) product unless otherwise noted. a) yield based on input of **1**; b) yield based on input of phenol; c) 0.43 mole% CuCl was used; d) 1 mole% CuCl was used; e) recrystallized from hexane/ethyl acetate.

Reaction conditions used for each reagent:

1: Phenol (27.5 mmol), DBU (4.50 mL, 30.1 mmol), $CuCl_2 \cdot 2\ H_2O$ (4.7 mg, 28 μmol, 0.1 mole%), and **1** (2.56 g, 25 mmol) in CH_3CN (25 mL) at 0°C for 5 hours.

9: Phenol (25.2 mmol), DBU (5.0 mL, 33.4 mmol), $CuCl_2 \cdot 2\ H_2O$ (13 mg, 76 μmol, 0.3 mole%), and **9** (3.93 g, 27.6 mmol) in CH_3CN (24 mL) at 0°C for 24 hours.

11: Preparation of **4** by general procedure using trifluoroacetate **11**.

To a solution of 2-methyl-3-butyn-2-ol (4.88 g, 58.0 mmol) in anhydrous CH_3CN (30 mL) under argon and cooled in an ice-salt bath (-5°C) was added DBU (11.2 mL, 74.9 mmol). Trifluoroacetic anhydride (8.2 mL, 58.0 mmol) was added over a 25 minute period while keeping the temperature at less than 2°C. The resulting solution of **11** was allowed to stir at 0°C for 30 minutes before addition to the 4-cyanophenol solution.

To a solution of 4-cyanophenol (6.0 g, 50.4 mmol) in CH_3CN (30 mL) under argon and cooled in an ice-salt bath (-4°C) was added DBU (9.7 mL, 64.9 mmol) and $CuCl_2 \cdot 2\ H_2O$ (9.3 mg, 55 μmol, 0.1 mole%).

The solution of **11**, maintained at 0°C, was added to the 4-cyanophenol solution over a 40 minute period while keeping the temperature at ~0°C. After stirring for 5 hours at 0°C, the mixture was concentrated at reduced pressure and the residue was partitioned between water (50 mL) and toluene (300 mL). The organic fraction was washed with 1 N HCl (3 x 50 mL), 1 N NaOH (2 x 50 mL), 1 N $NaHCO_3$, and brine. After drying ($MgSO_4$), the solvent was removed at reduced pressure to give **4** as a pale yellow oil. Distillation (bulb to bulb, ~110°C, 0.25 mm Hg) gave **4** as a colorless solid (8.04 g, 86%).

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