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LETTERS

A novel route to 2-(dialkylaminomethyl)benzo[*b*]furans via a microwave-enhanced, solventless Mannich condensation–cyclization on cuprous iodide doped alumina

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Abstract—A microwave-enhanced, solventless Mannich condensation–cyclization sequence involving the reaction of *o*-ethynylphenol with secondary amines and *para*-formaldehyde on cuprous iodide doped alumina in the absence of solvents has been developed. The procedure generates 2-(dialkylaminomethyl)benzo[*b*]furans in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

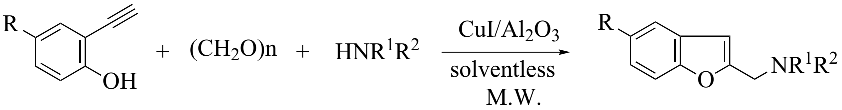
Benzo[*b*]furans and their derivatives have received attention in recent years because of their occurrence in natural substances and their physiological activity.[1] They are widely used as anti-tumor agents,[2] as ligands for the adenosine A_1 receptor,[3] and as calcium entry blockers.[4] General routes to benzo[*b*]furans involve reductive cyclization of ketoesters by low-valent titanium,[5] photochemical induced rearrangement of phosphate esters,[6] palladium-catalyzed Suzuki coupling of appropriate boronic acids with organic halides or triflates,[7] and palladium-catalyzed Sonogashira coupling of *o*-iodophenols and terminal alkynes.[8] No reports have appeared describing the synthesis of 2-substituted-benzo[*b*]furans using Mannich condensation reactions.

The traditional Mannich methods for synthesizing β-aminoketones or β-aminoalkyne often require drastic reaction conditions and utilize solvents such as dioxane or *N*,*N*-dimethylformamide. In addition, metal catalysts are required which can be difficult to handle and pose, along with the solvent, a number of waste handing problems.

We have found alumina to be a particularly useful reagent in organic synthesis because it can be modified in a variety of ways which enhance its reactivity. Alumina also obviates a number of environmental problems.[9] For example, using a commercially available alumina potassium fluoride mixture to which we added palladium powder or cupric chloride, we were able to carry out Suzuki, Sonogashira, and Glaser coupling reactions on a wide variety of aromatic moieties without the use of solvents.[10]

Microwave irradiation of organic reaction has gained in popularity in recent years since it was found to accelerate a wide variety of transformations.[11] A number of reports have appeared in which reactants are coated onto 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 savings as well as making it possible to carry out reactions in relatively simple glassware, such as open beakers and flasks.[12]

We wish to report a microwave-enhanced Mannich condensation–cyclization sequence involving *o*-ethynylphenol, secondary amines and *para*-formaldehyde on CuI-doped alumina in the absence of solvents, which generates 2-(dialkylaminomethyl)benzo[*b*]furans in good yields (Scheme 1).



Scheme 1.

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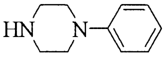
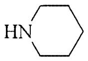
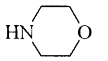
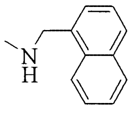
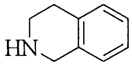
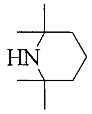
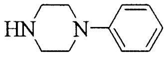
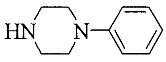
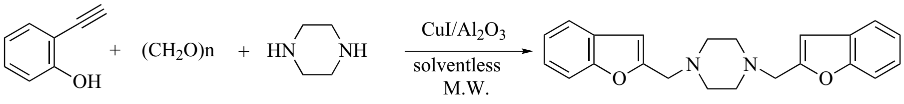
Table 1. Mannich condensation–cyclization reaction of *o*-ethnylphenol and its derivatives with secondary amines and *para*-formaldehyde

Entry	R	Amine	Yield (%)[a]
a	H		67
b	H	$(n\text{-}C_4H_9)_2NH$	66
c	H		70
d	H	$C_6H_5CH_2NHCH_3$	62
e	H		55
f	H		69
g	H		62
h	H	$(i\text{-}C_3H_7)_2NH$	56
i	H		52
j	H	$C_6H_5NHCH_3$	38
k	CH_3		64
l	CH_3CO		61

[a] Isolated yields.

Table 1 contains the results of our study. Under microwave irradiation and solvent free conditions, *o*-ethynylphenol (as well as *o*-ethynyl-*p*-methylphenol and *p*-acetyl-*o*-ethynylphenol), react smoothly with *para*-formaldehyde and a variety of secondary amines to afford the desired 2-(dialkylaminomethyl)benzo[*b*]furans in good yields. Interestingly, when *o*-ethynylphenol (2 equiv.) was allowed to react with *para*-formaldehyde (excess) and piperazine (1 equiv.), a bis-Mannich condensation–cyclization product was formed (40% yield, Scheme 2). A general procedure is illustrated for the preparation of 2-(dialkylaminomethyl)benzo[*b*]furans: *o*-ethynylphenol (0.118 g, 1.00 mmol) and a secondary amine (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 which had been punctured by an 18 gauge needle (to serve as a pressure relief valve), placed in the microwave oven and irradiated at 30% power for 5 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



Scheme 2.

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 eluent) to afford the desired 2-(dialkylaminomethyl)benzo[*b*]furan.

In conclusion, a reliable, rapid, and environmentally benign method for synthesizing 2-(dialkylaminomethyl)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 preforming the iminium species, and is not hampered by the heterogeneity of the reaction.

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