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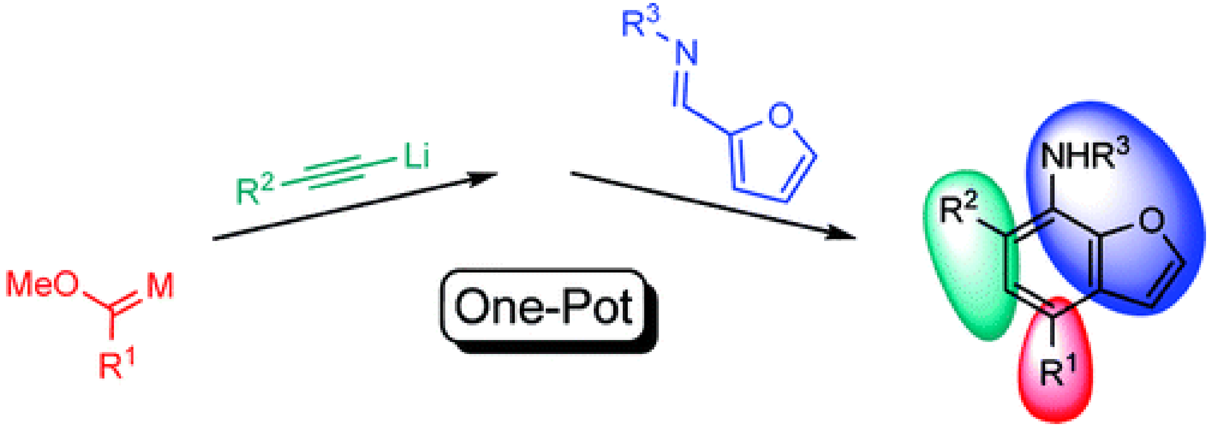
Institut des Sciences Moléculaires de Marseille
UMR 6263

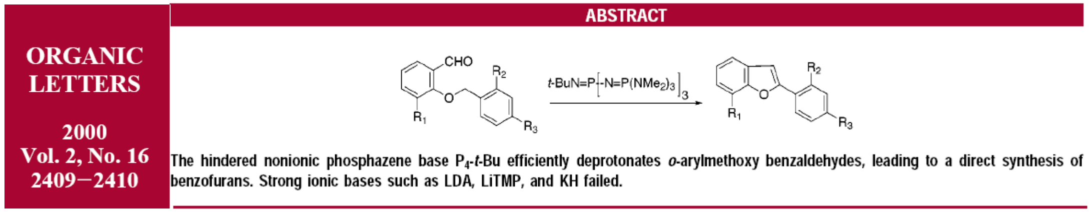
Regioselective Synthesis of 4,6,7-Trisubstitued Benzofurans



Barluenga, J.; Aránzazu, G.; Santamaría, J.; Tomás, M.

J. Am. Chem Soc., **2009**, Article ASAP

Previously in benzofuran synthesis…

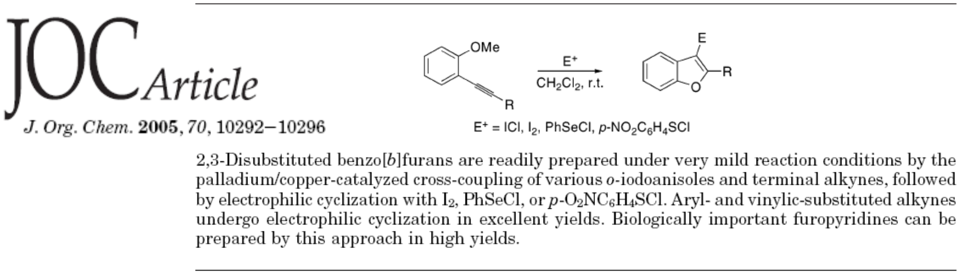


ORGANIC LETTERS

2000
Vol. 2, No. 16
2409−2410

ABSTRACT

The hindered nonionic phosphazene base P_4-*t*-Bu efficiently deprotonates *o*-arylmethoxy benzaldehydes, leading to a direct synthesis of benzofurans. Strong ionic bases such as LDA, LiTMP, and KH failed.

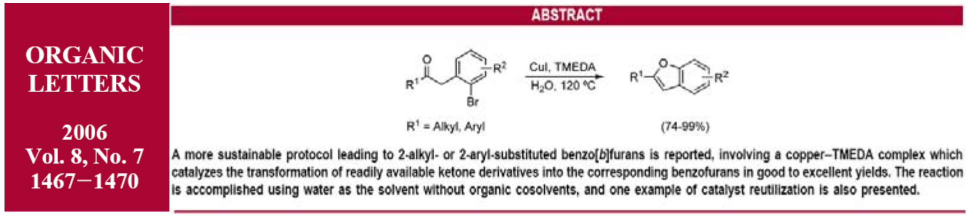


JOC *Article*

J. Org. Chem. **2005**, *70*, 10292−10296

E$^+$ = ICl, I_2, PhSeCl, *p*-$NO_2C_6H_4SCl$

2,3-Disubstituted benzo[*b*]furans are readily prepared under very mild reaction conditions by the palladium/copper-catalyzed cross-coupling of various *o*-iodoanisoles and terminal alkynes, followed by electrophilic cyclization with I_2, PhSeCl, or *p*-$O_2NC_6H_4SCl$. Aryl- and vinylic-substituted alkynes undergo electrophilic cyclization in excellent yields. Biologically important furopyridines can be prepared by this approach in high yields.



ORGANIC LETTERS

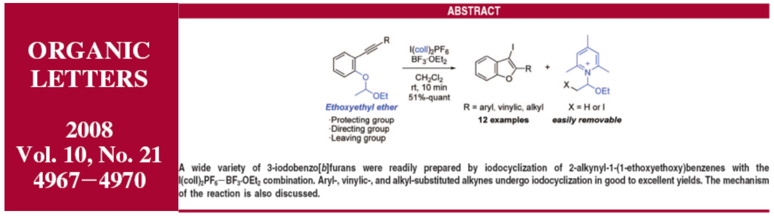
2006
Vol. 8, No. 7
1467−1470

ABSTRACT

R^1 = Alkyl, Aryl

(74-99%)

A more sustainable protocol leading to 2-alkyl- or 2-aryl-substituted benzo[*b*]furans is reported, involving a copper–TMEDA complex which catalyzes the transformation of readily available ketone derivatives into the corresponding benzofurans in good to excellent yields. The reaction is accomplished using water as the solvent without organic cosolvents, and one example of catalyst reutilization is also presented.



ORGANIC LETTERS

2008
Vol. 10, No. 21
4967−4970

ABSTRACT

Ethoxyethyl ether
·Protecting group
·Directing group
·Leaving group

R = aryl, vinylic, alkyl
12 examples

X = H or I
easily removable

A wide variety of 3-iodobenzo[*b*]furans were readily prepared by iodocyclization of 2-alkynyl-1-(1-ethoxyethoxy)benzenes with the I(coll)$_2$PF$_6$−BF_3-OEt_2 combination. Aryl-, vinylic-, and alkyl-substituted alkynes undergo iodocyclization in good to excellent yields. The mechanism of the reaction is also discussed.

Scope of the one-pot reaction

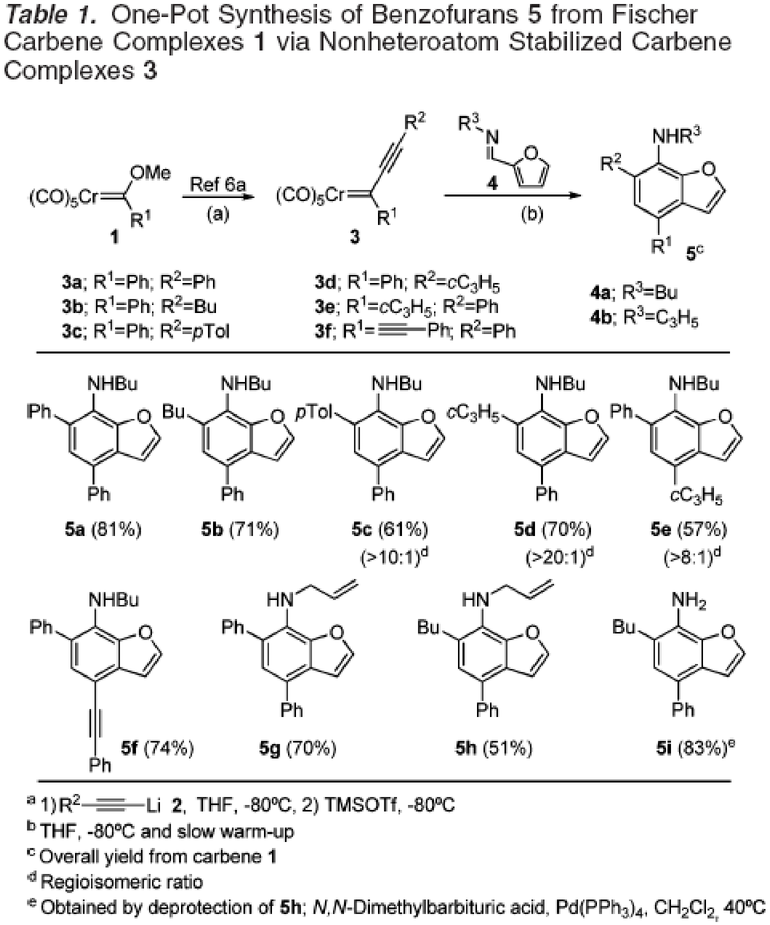


Table 1. One-Pot Synthesis of Benzofurans **5** from Fischer Carbene Complexes **1** via Nonheteroatom Stabilized Carbene Complexes **3**

3a; R^1=Ph; R^2=Ph
3b; R^1=Ph; R^2=Bu
3c; R^1=Ph; R^2=pTol
3d; R^1=Ph; R^2=cC_3H_5
3e; R^1=cC_3H_5; R^2=Ph
3f; R^1=$\equiv$—Ph; R^2=Ph
4a; R^3=Bu
4b; R^3=C_3H_5

5a (81%)
5b (71%)
5c (61%) (>10:1)[d]
5d (70%) (>20:1)[d]
5e (57%) (>8:1)[d]
5f (74%)
5g (70%)
5h (51%)
5i (83%)[e]

[a] 1) R^2—$\equiv$—Li **2**, THF, -80ºC, 2) TMSOTf, -80ºC
[b] THF, -80ºC and slow warm-up
[c] Overall yield from carbene **1**
[d] Regioisomeric ratio
[e] Obtained by deprotection of **5h**; *N,N*-Dimethylbarbituric acid, $Pd(PPh_3)_4$, CH_2Cl_2, 40ºC

Mechanistic proposal

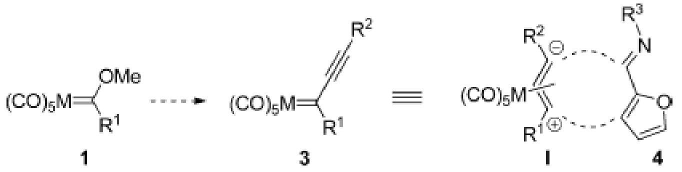
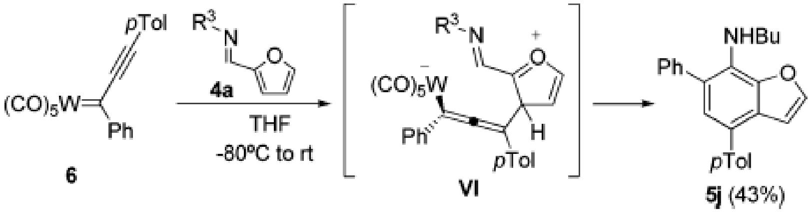
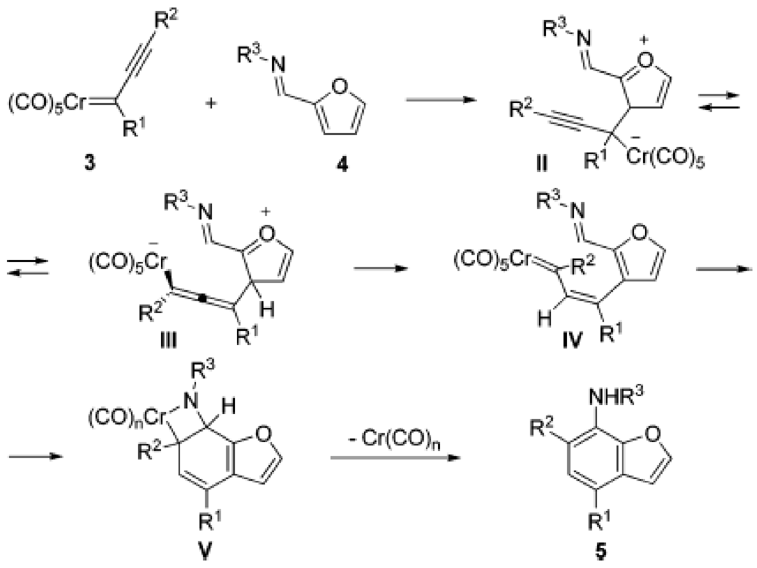


Figure 1. [3+3] Carbocyclization of nonstabilized alkynyl carbenes.

Scheme 2. Reverse Regioselectivity with Tungsten Carbene Complex **6**



Scheme 1. Mechanistic Proposal for the Formation of Benzofurans **5a−h**



Thank you for your attention.

Any question