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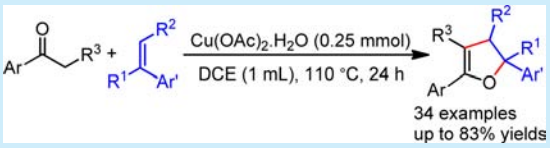
Radical Based Strategy toward the Synthesis of 2,3-Dihydrofurans from Aryl Ketones and Aromatic Olefins

Togati Naveen, Rajesh Kancherla, and Debabrata Maiti*

Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

S Supporting Information

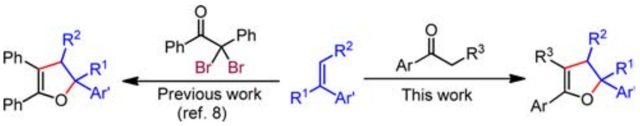
ABSTRACT: A copper-mediated annulation of aryl ketones with a wide range of aromatic olefins has been developed. This strategy allowed convenient access to 2,3-dihydrofuran derivatives. The versatility of the protocol is shown by synthesizing α-methyl dihydrofurans, which serve as an intermediate for the synthesis of vitamin B1. In addition, the applicability of the protocol in conjugated systems is demonstrated. A radical pathway was presumed and supported for annulation of aryl ketones with olefins.



Among the five-membered heterocycle derivatives, 2,3-dihydrofuran is one of the most important motifs present in a number of pharmaceuticals (e.g., aflatoxin B1, clerodin, etc.)[1] and natural products (e.g., azadirachtin, austocystin A, etc.).[1] The 2,3-dihydrofurans are also extremely useful synthetic intermediates in the preparation of highly functionalized tetrahydrofurans with good stereoselectivity.[2] These scaffolds are used in 1,3-dipolar cycloaddition reactions to synthesize heterocyclic compounds with different ring size and atoms.[3] Given the importance of 2,3-dihydrofurans in natural and synthetic substances, the development of a selective and straightforward intermolecular approach to construct polysubstituted dihydrofurans from simple and economical chemical reagents is still in great demand.[4−6]

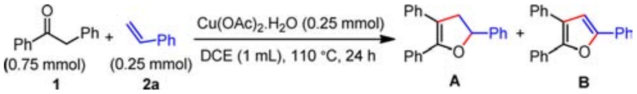
Alkenes have been recognized as important starting materials in synthetic chemistry because of their low cost and ready availability. Following our recent efforts to utilize alkene for generating value-added compounds,[7] we envisioned that these moieties can be employed for the synthesis of 2,3-dihydrofurans through carbon−carbon and carbon−oxygen bond formation. In this context, Fukuzawa reported the synthesis of 2,3-dihydrofurans starting from 2,2-dibromo-1,2-diphenylethanone and a styrene as the annulation partners (Scheme 1).[8] Although use of dibromo starting material limited the utility of this method,[8] it provided us the inspiration to synthesize 2,3-dihydrofuran from a simple ketone and an olefin. We envisioned that a radical intermediate generated at the α-position of the ketone will attack the styrene and subsequent cyclization will lead to substituted 2,3-dihydrofuran (*vide infra*).

Scheme 1. Synthesis of 2,3-Dihydrofuran from Olefin



Our initial efforts were focused on the reaction of deoxybenzoin with styrene by using Cu(OAc)$_2$. Upon extensive optimization (Table 1),[9] the expected dihydrofuran product **3a** was obtained in 85% (GC) yield (isolated, 83%) after stirring at 110 °C for 24 h using dichloroethane (DCE) as the solvent. No desired product was obtained in the absence of Cu(OAc)$_2$ (Table 1, entry 17). Attempts to reduce the reaction time resulted in lower yields.[9]

Table 1. Reaction Optimization



entry	change of the standard conditions	A:B[a]	GC yield of **A** (%)
1	**standard conditions**	**10:1**	**85**
2	CuCl	7:1	48
3	CuOAc	9:1	70
4	CuBr	8:1	19
5	CuF$_2$·H$_2$O	7:1	34
6	0.1 mmol of Cu(OAc)$_2$·H$_2$O	3:1	40
7	0.2 mmol of Cu(OAc)$_2$·H$_2$O	5:1	70
8	0.3 mmol of Cu(OAc)$_2$·H$_2$O	6:1	75
9	0.25 mmol of ketone	6:1	40
10	0.5 mmol of ketone	7:1	52
11	1.0 mmol of ketone	8:1	61
12	0.5 mmol of styrene	8:1	63
13	DMSO	2:1	6
14	CH$_3$CN	3:1	35
15	benzene	2:1	25
16	1,4-dioxane	1:1	8
17	no copper salts	–	0

[a] The ratio of 2,3-dihydrofuran (**A**) and its respective furan (**B**) is measured based on GC analysis of the crude reaction mixture.

Under the optimized reaction conditions, various styrenes were tested to access the expected dihydrofuran products

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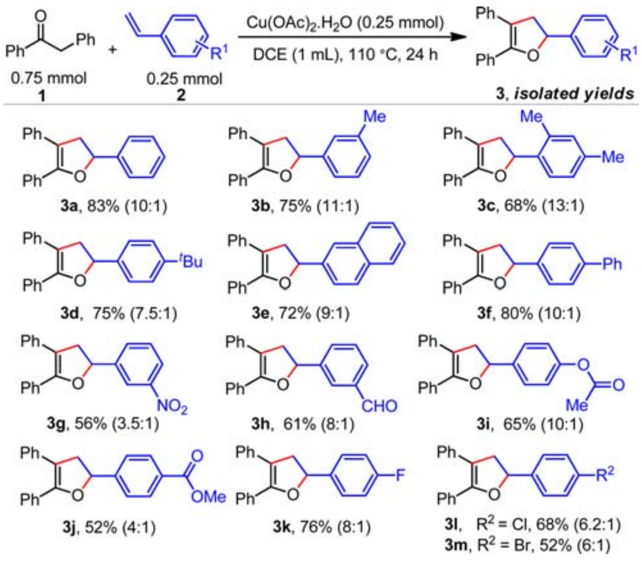
(Scheme 2). Both electron-withdrawing and -donating styrenes were successfully employed, and it is noteworthy that steric effects had little influence on this reaction. Regardless of the substitution pattern of styrenes (*ortho*, *meta*, or *para*) used in the reaction, expected dihydrofuran products were obtained. Several important functional groups such as $-NO_2$ (**3g**), −CHO (**3h**), $-OCOCH_3$ (**3i**), $-COOCH_3$ (**3j**), and halogens (−F, −Cl, and −Br, **3k−m**) were tolerated under the current reaction conditions, which allow high diversity in the synthesis of functionalized dihydrofurans. It was also found that substituted styrenes with electron-donating groups such as methyl (**3b**) and *tert*-butyl (**3d**) delivered better yields than those obtained with electron-withdrawing groups (**3g−j**).

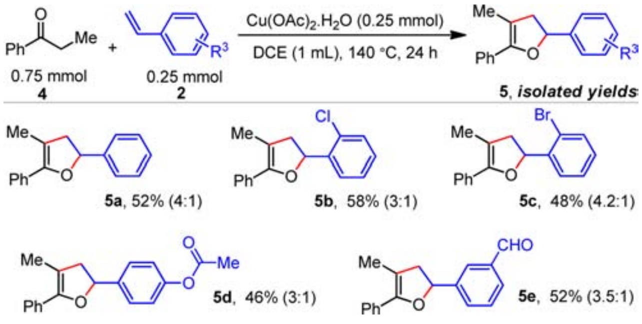
Scheme 2. Scope with Different Styrenes[a]



[a] Isolated yields of **3**. The ratio of 2,3-dihydrofuran (**3**) and respective furan is measured based on GC analysis of the crude reaction mixture (see Table 1).

Next, we tested propiophenone with styrenes (Scheme 3) bearing halogens (−Cl, −Br, **5b** and **5c**) and electron-withdrawing substituents ($-OCOCH_3$, −CHO, **5d** and **5e**). All of them gave the corresponding dihydrofurans in moderate to good yields. Unfortunately, dialkyl ketones did not give the desired product under the standard reaction conditions.

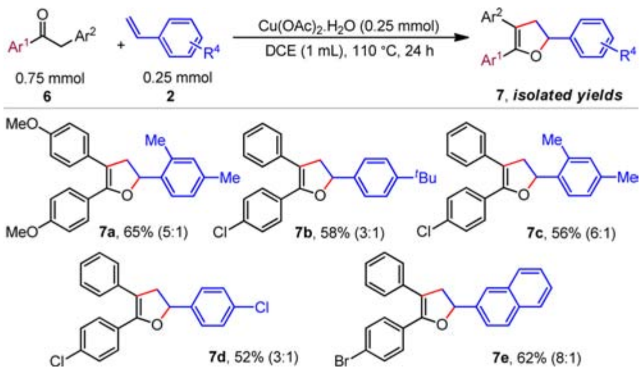
Scheme 3. Scope with Propiophenone[a]



[a] Isolated yields of **5**. The ratio of 2,3-dihydrofuran (**5**) and respective furan is measured based on GC analysis of the crude reaction mixture (see Table 1).

To further explore the substrate scope, different aryl ketones were investigated (Scheme 4). Deoxybenzoin bearing substituents such as methoxy (**6a**), chloro (**6b−d**), and bromo (**6e**) delivered the corresponding dihydrofurans (**7a−e**) in preparatively useful yields.

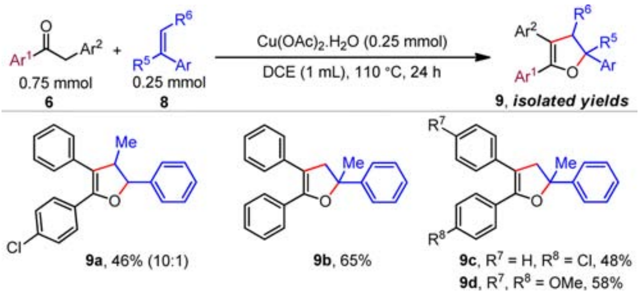
Scheme 4. Scope with Different α-Arylketones[a]



[a] Isolated yields of **7**. The ratio of 2,3-dihydrofuran (**7**) and respective furan is measured based on GC analysis of the crude reaction mixture (see Table 1).

Since α-methyl dihydrofuran serves as an intermediate for the synthesis of vitamin B_1,[10] we thought to synthesize such scaffolds following this method. Interestingly, the present method can be extended to synthesize α-methyl dihydrofurans (**9b−d**) from α-methylstyrene (Scheme 5). In the case of (*Z*)-β-methylstyrene (**8a**), only the *trans*-isomer of the dihydrofuran (**9a**) was obtained.

Scheme 5. Scope with α- and β-Methyl Styrenes[a]



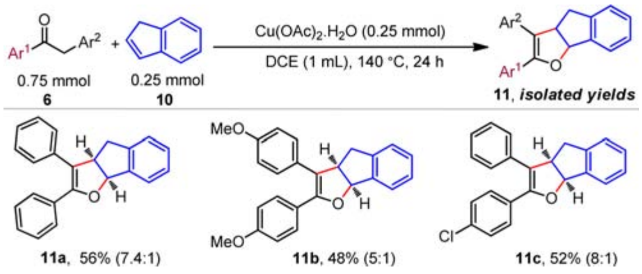
[a] Isolated yields of **9**. The ratio of 2,3-dihydrofuran (**9a**) and respective furan is measured based on GC analysis of the crude reaction mixture (see Table 1).

Replacing the styrene with a cyclic olefin such as indene (**10**) also afforded the dihydrofurans (**11a−c**) in moderate to good yields (Scheme 6). These dihydrofuran-fused cycloalkanes are important for the synthesis of biologically active natural products, such as aflatoxin, asteltoxin, etc.[11] Different aryl ketones with methoxy (**6b**) and chloro (**6c**) substituents were also well tolerated under the current reaction conditions.

Furthermore, we thought to replace the styrene with (1*E*,3*E*)-1,4-diphenylbuta-1,3-diene (**12**) under the optimized reaction conditions (Scheme 7). Formation of 2-styryl-2,3-dihydrofurans (**13a−d**) demonstrated the applicability of the protocol in conjugated systems.

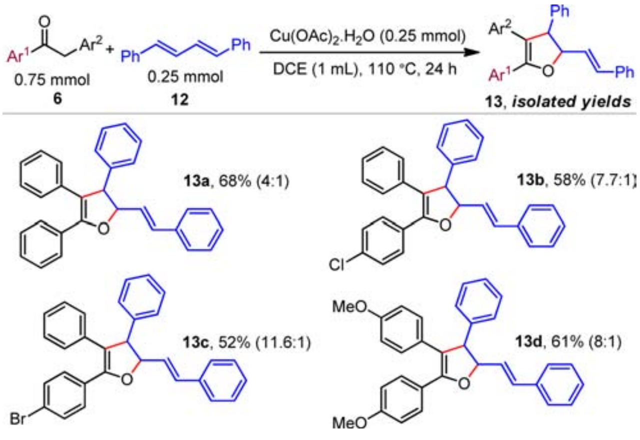
The addition of 2 equiv of DTBP (di-*tert*-butylperoxide) under the standard conditions resulted in a negligible amount

Scheme 6. Scope with Indene[a]



[a]Isolated yields of **11**. The ratio of 2,3-dihydrofuran (**11**) and respective furan is measured based on GC analysis of the crude reaction mixture (see Table 1).

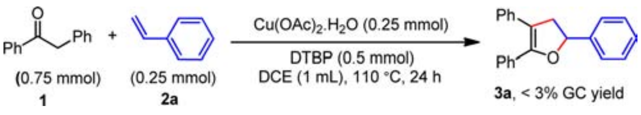
Scheme 7. Scope with Conjugated Olefin[a]



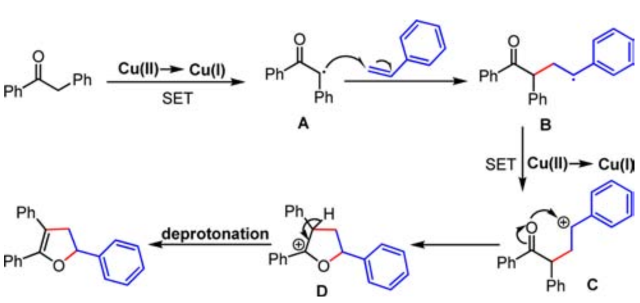
[a]Isolated yields of **13**. The ratio of 2,3-dihydrofuran (**13**) and respective furan is measured based on GC analysis of the crude reaction mixture (see Table 1).

of desired product formation (Scheme 8). This experiment is likely supporting a radical pathway to be operative in the present case. A radical based mechanism has been outlined in Scheme 9. Formation of carbon centered radical **A** is proposed from aryl ketone via single electron transfer (SET). The Cu(I) formed in the reaction is likely to be oxidized to Cu(II) via Cu(I)/O_2 interaction.[12] Addition of **A** to the β-position of the styrene will lead to **B**. The subsequent single electron transfer and intramolecular cyclization will produce **D**, which will form 2,3-dihydrofuran upon deprotonation.

Scheme 8. Radical Scavenger Experiment



Scheme 9. Plausible Mechanism



In summary, we have demonstrated a copper-mediated annulation of aryl ketones and aromatic olefins. This reaction provides a novel synthetic route to 2,3,5-tri-, 2,3,5,5′-tetra-, and 2,3,4,5-tetrasubstituted dihydrofurans from readily available starting materials.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dmaiti@chem.iitb.ac.in.

Notes

The authors declare no competing financial interest.

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