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ARTICLE

Preparation of polysubstituted dihydrofurans through a $PhI(OAc)_2$-promoted haloenolcyclization of olefinic dicarbonyl compounds

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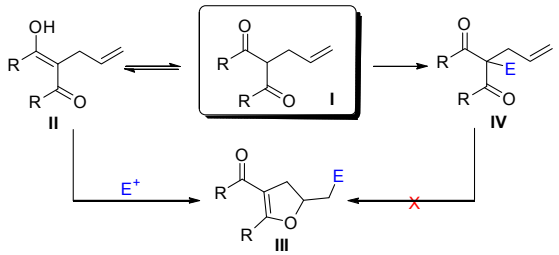
A metal-free cyclization of olefinic dicarbonyl compounds for the synthesis of various 5-halomethyl-4,5-dihydrofurans is presented. Using (diacetoxyiodo)benzene as the reaction promoter and halotrimethylsilane as the halogen source, the intramolecular haloenolcyclization of the 2-allyl-1,3-diketones smoothly proceeded, leading to the corresponding 5-halomethyl-4,5-dihydrofurans in good to excellent isolated yields. Moreover, the resulting 5-iodomethyl products could be converted to functionalized furans in almost quantitative yields by treatment with DBU followed by acid-catalyzed rearrangement. The reactions could be carried out on a gram scale and did not require harsh reaction conditions. The good isolated yields, mild conditions, and operational simplicity make this reaction a viable method for the construction of different dihydrofuran and furan structures.

Introduction

Dihydrofurans are key structural motifs in several biologically interesting skeletons and are important subunits in different natural products.[1] Moreover, these functional groups are also frequently employed as synthons in natural product synthesis, medicinal chemistry and diversity-oriented synthesis[2] since the reactive enol ether moiety in dihydrofurans can be further manipulated by various reactions such as aromatization to furans or ring opening to generate linear chain compounds. To this end, a substantial amount of effort has been devoted to the development of novel methods for the synthesis of these compounds.[3]

2-Allyl-1,3-diketones **I**, which contain an acidic proton alpha to the carbonyl functionality due to their strong electron-withdrawing effect, could isomerize to enol **II** and undergo an electrophile-mediated enolcyclization, furnishing highly functionalized dihydrofurans **III** (Scheme 1, left). Therefore, this strategy has been widely applied to for the construction of dihydrofuran rings due to its step economy. For example, Antonioletti and coworkers reported the iodoenoletherification of 2-alkenyl-substituted 1,3-dicarbonyl compounds, leading to the iodo-dihydrofurans in high yields.[4] Huang et al. prepared compounds of this class via polymer-supported, selenium-induced electrophilic cyclizations of α-allyl-substituted 1,3-dicarbonyl compounds followed by cleavage of the selenium linkers with CH_3I–NaI in DMF.[5] Terent'ev et al. developed a one-pot procedure for the construction of bicyclic compounds containing 1,2-dioxolane and tetrahydrofuran ring by the reaction of 2-allyl-1,3-diketones with the I_2/H_2O_2 system.[6] In addition, other substrates such as α-allyl-substituted β-keto sulfones,[7] α-allyl-substituted β-ketoesters,[8] β-enamino esters,[9] β-enamino ketones,[10] and β-phosphonate ketones[11] have also been employed in this type of reaction to prepare dihydrofurans.



Scheme 1. Schematic representation of the cyclization of 2-allyl-1,3-diketone.

Despite these advances, general methods for the preparation of various halogenated dihydrofurans, bromomethyl dihydrofurans in particular, are still limited. This can be attributed to the use of olefinic 1,3-dicarbonyl compounds **I**, which are highly susceptible to halogenation α to the carbonyl groups (Scheme 1, right).[12] The resulting α-halogenated dicarbonyl compound **IV** could not be converted into the corresponding dihydrofurans.[13] Furthermore, a superstoichiometric amount of electrophile is usually needed for most reactions of this type, even for well-developed iodocyclization.[4, 7, 8c, 8g] These drawbacks more or less limited

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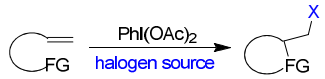
the application of these methods in the preparation of structurally diverse dihydrofuran compounds. Nonetheless, herein we report an efficient, practical and scalable halocyclization of olefinic 1,3-dicarbonyl compounds to afford to 2,3,5-trisubstituted dihydrofurans as a continuation of our investigation of the cyclization of unfunctionalized olefins.[14]

Results and Discussion

Recently, we have shown that (diacetoxyiodo)benzene can be used to promote haloheterocyclizations of different unfunctionalized olefins (Scheme 2). In the presence of $PhI(OAc)_2$ and suitable halogen sources, a variety of halocyclizations could be realized, giving the corresponding halogenated products in good to excellent isolated yields.[14b, 14d]

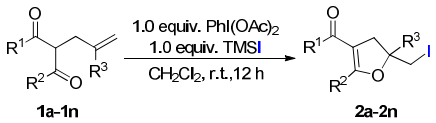


FG = NHR, OH, COOH

Scheme 2. $PhI(OAc)_2$-promoted intramolecular haloheterocyclizations.

As an extension of our ongoing work toward the cyclization of unactivated olefins and in analogy to the reactions mentioned above, we envisage that haloenolcyclization of olefinic 1,3-dicarbonyl compounds could be realized by the utilization of a previously developed protocol. Based on our previous results, we first examined a $PhI(OAc)_2$/TMSI system for the cyclization of 2-allyl-1,3-diphenylpropane-1,3-dione (**1a**). To our delight, under standard conditions, the reaction proceeded readily and provided desired dihydrofuran **2a** a 91% yield. No reaction occurred in the absence of $PhI(OAc)_2$ or TMSI. Encouraged by these results, other dicarbonyl compounds **1b**–**1m** were then subjected to the same conditions to test the scope of the reaction, and the results are summarized in Table 1. As these results showed, all reactions occurred in a clean fashion, giving exclusively the expected Markovnikov products. Dicarbonyl substrates with either electron-rich substituents or electron-deficient aryl substituents all gave the expected products in good isolated yields (**2a**-**2f**). Alkyl diketones such as **1g** also worked well in the current reaction system, and corresponding 4,5-dihydrofuran **2g** was obtained in good yield. Notably, the cyclization of 2-allyl-1-phenyl-1,3-butanedione led to a mixture of two isomers (**2h**/**2h'**) in a 2:3 ratio. The same cyclization in Huang's report led to exclusive incorporation of the benzoyl group into the furan ring to form 3-acetyl-5-iodomethyl-2-phenyl-4,5-dihydrofuran (**2h**) in 79% yield.[5] Interestingly, α-allylcyclohexane-1,3-diones could smoothly undergo iodocyclization, affording 2-iodomethyltetrahydrobenzofuran-4-one (**2i**) in 73%, and no further aromatization to the benzofuran was observed, probably due to the mild reaction conditions.[15] Substituents on the C=C double bonds showed little impact on the reaction outcome, and the products could be isolated in satisfactory yields (**2j** and **2k**). Bicyclic product **2k** exhibited a *cis*-fused ring.[16] The *cis* relative configuration of the rings, as well as the *trans* relationship between the iodine atom and the ether oxygen atom in **2k**, is a consequence of the cyclization proceeding through a kinetically controlled *trans*-diaxial addition to the double bond.[17] Preparation of 3,4-dihydro-2*H*-pyrans **2l** was also possible using a homoallylic diketone as the starting material. Finally, alkenyl-substituted β-ketoesters were good candidates for this transformation (**2m**), further highlighting the generality and great potential of the developed method.

Table 1. Substrate scope of $Ph(OAc)_2$-mediated iodoenolcyclization



1a-1n **2a-2n**

Entry	Substrate	Product	Isolated Yield
1	$R^1 = R^2$ = Ph (**1a**)	**2a**	91%
2	$R^1 = R^2$ = 4-MeOPh (**1b**)	**2b**	91%
3	$R^1 = R^2$ = 4-MePh (**1c**)	**2c**	86%
4	$R^1 = R^2$ = 4-FPh (**1d**)	**2d**	76%
5	$R^1 = R^2$ = 4-ClPhI (**1e**)	**2e**	80%
6	$R^1 = R^2$ = 4-BrPh (**1f**)	**2f**	81%
7	$R^1 = R^2$ = Et (**1g**)	**2g**	70%
8	**1h**	**2h** 31% + **2h'** 49%	
9	**1i**	**2i**	73%
10	**1j**	**2j**	86%
11	**1k**	**2k**	80%
12	**1l**	**2l**	88%
13	**1m**	**2m**	76%

Reaction conditions: The reaction was carried out in an open air system with 0.5 mmol of substrate, 1.0 mmol of $PhI(OAc)_2$ and 1.0 mmol of TMSI in 5 mL of DCM.

The scalability of the developed methodology was demonstrated by the gram-scale synthesis of dihydrofuran **2a**.

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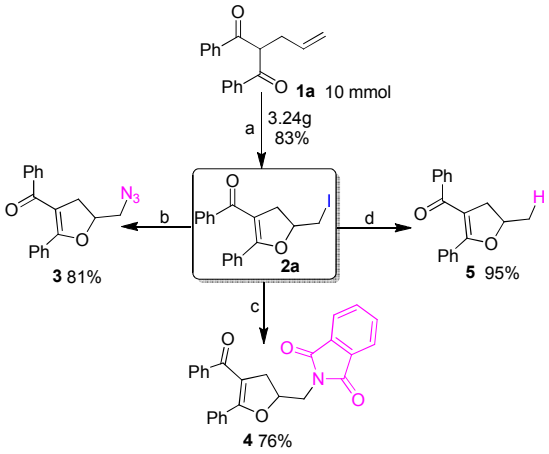
Iodocyclization of 2-allyl-1,3-diphenylpropane-1,3-dione (**1a**) was carried out on a 10-mmol scale, and product **2a** was obtained in 83% isolated yield (Scheme 3). Moreover, the C–I bond in **2a** provides easy access to a variety of useful functional groups. For example, the iodine atom in **2a** could be replaced by different nucleophiles, such as azide (**3**) and phthalimide (**4**), under mild conditions. Furthermore, the C–I bond in **2a** could also be easily cleaved via tributylstannane reduction. When **2a** was treated with AIBN/nBu$_3$SnH at 100 °C for 12 h in toluene, compound **5** could be obtained in an almost quantitative isolated yield.

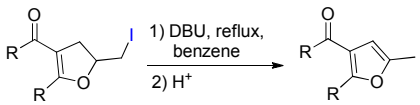


Conditions: (a) **1a** (10 mmol), PhI(OAc)$_2$ (10 mmol), TMSI (10 mmol), DCM, r.t., 24 h. (b) **2a**, NaN_3 (2.0 equiv.), DMF, r.t, 8 h;. (c) **2a**, phthalimide (1 equiv.), K_2CO_3 (2 equiv.), DMF, 80 °C, 12 h. (c) **2a**, AIBN (0.05 equiv.), nBu$_3$SnH (3 equiv.), toluene, 100 °C, 12 h.

Scheme 3. Gram-scale iodocyclization and derivatization of dihydrofurans **2a** to different bioactive structures.

To further demonstrate the synthetic value of the PhI(OAc)$_2$/TMSI system in the construction of diversely functionalized furan derivatives, selected iodomethyl dihydrofurans were dehydroiodinated by treatment with a nonnucleophilic, hindered tertiary amine (DBU) at reflux condition in benzene. The reaction gave the corresponding alkylidenedihydrofurans, which could be converted to furan derivatives through an acid-catalyzed isomerization. As shown in Table 2, furans **6** were obtained in almost quantitative isolated yields. It was noted that bicyclic substrate **2k** gave a different result. In this case, **2k** produced exclusively the product of the *anti*-elimination. Resulting product **6h** cannot aromatize to the furan under acidic conditions.[4b, 4e, 18]

Table 2. Synthesis of polysubstituted furans



Entry	Substrate	Product	Isolated Yield
1	R = Ph (**2a**)	**6a**	89%
2	R = 4-MeOPh (**2b**)	**6b**	93%
3	R = 4-MePh (**2c**)	**6c**	90%
4	R = 4-FPh (**2d**)	**6d**	95%
5	R = 4-ClPh (**2e**)	**6e**	94%
6	R = 4-BrPh (**2f**)	**6f**	95%
7	**2i**	**6g**	90%
8	**2k**	**6h**	96%
9	**2n**	**6i**	96%

Reaction conditions: The reaction was carried out with 0.5 mmol of substrate and 1.0 mmol of DBU in 5 mL of benzene.

Compared to the well-documented intramolecular iodoenolcyclizations of different 2-alkenyl-1,3-dicarbonyl compounds, the bromine variant of this type of reaction is less investigated, and only a few examples have been reported. For instance, Mphahlele et al. discovered that α-allylcyclohexane-1,3-diones could undergo pyridinium tribromide-promoted bromocyclization and afford a mixtures of 2-bromomethyltetrahydrobenzofuran-4-ones and 3-bromotetrahydrobenzopyran-5-ones.[15] Yeung and coworkers recently reported an enantioselective bromocyclization of olefinic 1,3-dicarbonyl compounds, but the substrates were limited to substituted alkenes.[13] Motivated by the scant attention paid in the literature to the bromoenolcyclization of olefinic dicarbonyl compounds, the bromine variant of the reaction was next studied using the same method. As shown in Scheme 4, different bromomethyl dihydrofurans could be obtained in acceptable isolated yields using TMSBr as the bromine source.[19] Resulting dihydrofurans **7** are valuable building blocks and can be converted to synthetically valuable keto-benzoates and 1,2-diketo products via simple derivatizations.[20]

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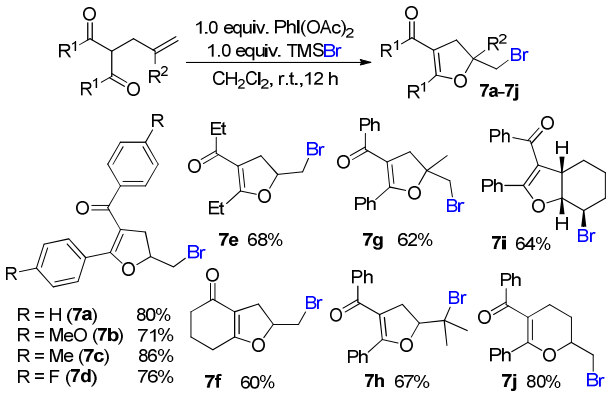
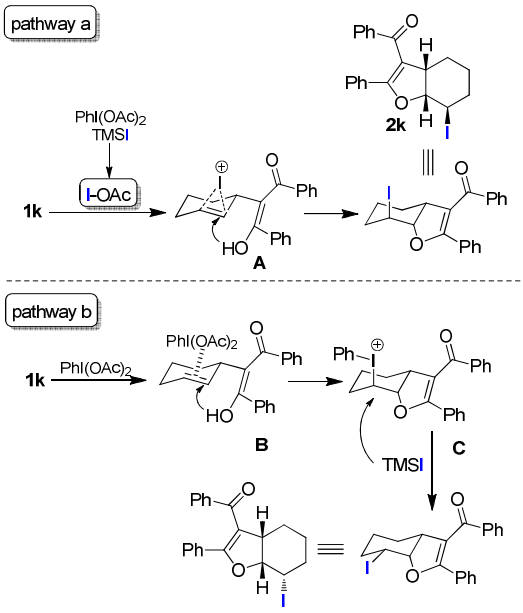


Scheme 4. $Ph(OAc)_2$-promoted bromoenolcyclization of olefinic dicarbonyl compounds.

On the basis of the relative configuration of **2k** and previous literature reports, a preliminary reaction pathway was proposed (Scheme 5, pathway a). First, the substrate **1k** formed an iodonium species **A** by electrophilic addition of IOAc, which was generated *in situ* by oxidation of $Ph(OAc)_2$ with TMSI.[21] Subsequently, an intramolecular nucleophilic attack of oxygen atom on the iodinium three-membered ring produced **2k**. The *trans* relative configuration between the iodine atom and the ether oxygen atom in **2k** arose from the *anti*-attack of oxygen atom on the double bond.[4e, 8f, 9, 17] An alternative pathway (Scheme 5, pathway b) involving activation of alkene by $PhI(OAc)_2$ followed by intramolecular nucleophilic attack of oxygen atom and nucleophilic substitution by TMSI seemed unlikely since two S_N2 processes would lead to *cis* relative configuration of the iodine atom and the oxygen atom in product. In addition, NMR experiments were also carried out to study the possible interaction between $PhI(OAc)_2$ and the olefinic part of the substrate. However, no significant chemical shift change was observed when **1a** was allowed to mix with $Ph(OAc)_2$.[22] This results indicated that the substrate interaction with the hypervalent iodine reagent generating species **B**/**C** is less possible.



Scheme 5. Plausible mechanism for iodoenolcyclization

Conclusions

The results shown in this work extend the utility of the (diacetoxyiodo)benzene-promoted cyclizations of unfunctionalized olefins. Using 1.0 equiv. of $PhI(OAc)_2$ as the reaction promoter and 1.0 equiv. of TMSX (X = I and Br) as the halogen source, 5-halomethyl-4,5-dihydrofuran products could be obtained in good to excellent isolated yields. The reaction could be carried out on a gram scale, and the iodide substituent could be easily converted to other functional groups via conventional methods. Moreover, the resulting iodomethyl dihydrofurans could be dehydroiodinated by treatment with DBU in refluxing benzene to afford functionalized furans in almost quantitative yields. Thus, we believe that the methodology described here will provide an effective route to a variety of functionalized dihydrofurans and furans. Efforts towards an asymmetric variant of this transformation are currently underway in our laboratory.

Experimental section

General information: Reagents were used as received without further purification unless otherwise indicated. Solvents were dried and distilled prior to use. Reactions were monitored with thin layer chromatography using silica gel GF_{254} plates. Organic solutions were concentrated in vacuo with a rotavapor. Flash column chromatography was performed using silica gel (200–300 meshes). Petroleum ether used had a boiling point range of 60–90 °C. Melting points were measured on a digital melting point apparatus without correction of the thermometer. Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) at 400 MHz (100 MHz for ^{13}C) in $CDCl_3$. Chemical shifts were reported in ppm (δ) using TMS as internal standard, and

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spin–spin coupling constants (*J*) were given in Hz. High resolution mass spectrometry (HRMS) analyses were carried out on an FTICR HR-ESI-MS.

General procedure for the preparation of 5-iodomethyl-4,5-dihydrofurans: The reaction was carried out in an open air system. In a 20 mL sealed tube were added olefinic 1,3-dicarbonyl compounds (0.5 mmol), $PhI(OAc)_2$ (0.5 mmol), and TMSI (0.5 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 12 h. CH_2Cl_2 (10 mL) was then added, and the mixture was washed with aqueous $Na_2S_2O_3$. The combined organic layer was dried (Na_2SO_4) and concentrated to give crude residue, which was purified by flash column chromatography to give the corresponding products.

(5-(Iodomethyl)-2-phenyl-4,5-dihydrofuran-3-yl)(phenyl)methanone (**2a**). Compound **2a** was prepared according to the general procedure and isolated as a colorless solid (178 mg, 91% yield) after flash column chromatography (petroleum ether/ethyl acetate = 15/1); mp = 97.5–99.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.48 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.18 (m, 4H), 7.11 (d, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 4.94 – 4.87 (m, 1H), 3.55 – 3.49 (m, 3H), 3.11 (dd, *J* = 15.5, 7.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 193.2, 164.8, 138.8, 131.3, 130.1, 129.8, 129.3, 128.9, 127.7, 111.7, 80.0, 39.2, 8.7. Spectral data are in agreement with literature values.[5]

General procedure for nucleophilic substitution of 2a. Compound **2a** was dissolved in 2 mL of DMF, the nucleophile of interest was added, and the reaction mixture was stirred for a given time. Then 20 mL of CH_2Cl_2 was added, and the reaction mixture was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to give the corresponding product.

(5-(Azidomethyl)-2-phenyl-4,5-dihydrofuran-3-yl)(phenyl)methanone (**3**). Compound **3** was prepared according to the general procedure and isolated as a colorless oil (124 mg, 81% yield) after flash column chromatography (petroleum ether/ethyl acetate = 15/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.48 (d, *J* = 8.2 Hz, 2H), 7.26 – 7.19 (m, 4H), 7.13 – 7.07 (m, 4H), 5.09 – 5.02 (m, 1H), 3.62 (d, *J* = 5.0 Hz, 2H), 3.44 (dd, *J* = 15.3, 10.4 Hz, 1H), 3.13 (dd, *J* = 15.3, 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 193.2, 164.7, 138.7, 131.4, 130.2, 129.6, 129.3, 128.9, 127.7, 111.7, 80.3, 54.5, 35.9. HRMS–ESI: calc. for $[C_{18}H_{15}N_3O_2+H]^+$: m/z =306.1243, found: 306.1241.

2-((4-Benzoyl-5-phenyl-2,3-dihydrofuran-2-yl)methyl)isoindoline-1,3-dione (**4**). Compound **4** was prepared according to the general procedure and isolated as a colorless solid (155 mg, 76% yield) after flash column chromatography (petroleum ether/ethyl acetate = 60/1) ; mp = 132-134 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.99 – 7.85 (m, 4H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.22 – 7.15 (m, 3H), 7.11 – 7.03 (m, 3H), 5.21 – 7.17 (m, 1H), 4.30 (dd, *J* = 14.2, 9.0 Hz, 1H), 3.88 (dd, *J* = 14.2, 3.8 Hz, 1H), 3.58 (dd, *J* = 15.3, 10.3 Hz, 1H), 3.06 (dd, *J* = 15.3, 5.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 193.3, 168.3, 165.4, 132.7, 132.0, 131.2, 130.0, 129.8, 129.6, 128.9, 127.7, 123.5, 111.5, 78.6, 41.7, 36.2. HRMS–ESI: calc. for $[C_{26}H_{19}NO_4+H]^+$: m/z = 410.1392, found:410.1384.

(5-Methyl-2-phenyl-4,5-dihydrofuran-3-yl)(phenyl)methanone (**5**). To a 100 mL flask was added tributyltinhydride (1.5 mmol), AIBN (0.025 mmol), **2a** (0.5 mmol) and 20 mL of toluene. The resulting solution was refluxed at 100 °C for 12 h. The residue obtained by concentration was purified by flash column chromatography to give the **5** as a colorless oil (88 mg, 92% yield) after flash chromatography. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.34 (d, *J* = 8.4 Hz, 2H), 7.15 - 7.03 (m, 4H), 7.00 – 6.94 (m, 4H), 4.97 - 4.80 (m, 1H), 3.31 (dd, *J* = 14.7, 9.5 Hz, 1H), 2.87 (dd, *J* = 14.7, 8.2 Hz, 1H), 1.46 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 188.9, 161.2, 134.5, 126.2, 125.6, 125.2, 124.6, 124.1, 122.9, 107.3, 74.3, 35.3, 16.8. Spectral data are in agreement with literature values.[23]

General procedure for the preparation of furans: The mixture of iodomethyl dihydrofurans (0.5 mmol) and DBU (2 mmol) was stirred under nitrogen in 5 mL of benzene for 12 h at 60 °C. CH_2Cl_2 (10 mL) was then added, and the mixture was washed with diluted HCl. A few drops of H_2SO_4 (10 M) were added and the solution was stirred at room temperature until the completion of the reaction (TLC monitoring, usually 5 minutes). Then the solution was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated to give crude residue, which was purified by flash column chromatography to give the corresponding products.

(5-Methyl-2-phenylfuran-3-yl)(phenyl)methanone (**6a**). Compound **6a** was prepared according to the general procedure and isolated as a colorless oil (116 mg, 89% yield) after flash column chromatography (petroleum ether/ethyl acetate = 15/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.73 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.36 (m, 1H), 7.28 – 7.24 (m, 1H), 7.23 – 7.13 (m, 3H), 6.20 (d, *J* = 1.0 Hz, 1H), 2.29 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 190.9, 153.5, 150.1, 137.2, 131.6, 129.0, 128.6, 127.5, 127.2, 126.2, 120.7, 108.7, 12.4. Spectral data are in agreement with literature values.[24]

General procedure for the preparation of 5-bromomethyl-4,5-dihydrofurans: The reaction was carried out in an open air system. In a 20 mL sealed tube were added olefinic 1,3-dicarbonyl compounds (0.5 mmol), $PhI(OAc)_2$ (0.5 mmol), and TMSBr (0.5 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 12 h. CH_2Cl_2 (10 mL) was then added, and the mixture was washed with aqueous $Na_2S_2O_3$. The combined organic layer was dried (Na_2SO_4) and concentrated to give crude residue, which was purified by flash column chromatography to give the corresponding products.

(5-(Bromomethyl)-2-phenyl-4,5-dihydrofuran-3-yl)(phenyl)methanone (**7a**). Compound **7a** was prepared according to the general procedure and isolated as a colorless oil (138 mg, 80% yield) after flash column chromatography (petroleum ether/ethyl acetate = 15/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.47(d, *J* = 8.4 Hz, 2H), 7.27 – 7.18 (m, 4H), 7.11 (d, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 7.3 Hz, 2H), 5.13 – 5.16 (m,

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1H), 3.71 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.68 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.52 (dd, *J* = 15.4, 10.2 Hz, 1H), 3.21 (dd, *J* = 15.4, 7.0 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm= 193.2, 165.0, 138.8, 131.3, 130.1, 129.6, 129.3, 128.9, 127.7, 127.7, 111.7, 79.8, 37.5, 34.6. HRMS–ESI: calc. for $[C_{18}H_{15}BrO_2+H]^+$: m/z = 343.0334, found: 343.0323.

Conflicts of interest

There are no conflicts to declare.

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