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A practicable synthesis of 2,3-disubstituted 1,4-dioxanes bearing a carbonyl functionality from α,β-unsaturated ketones using the Williamson strategy†

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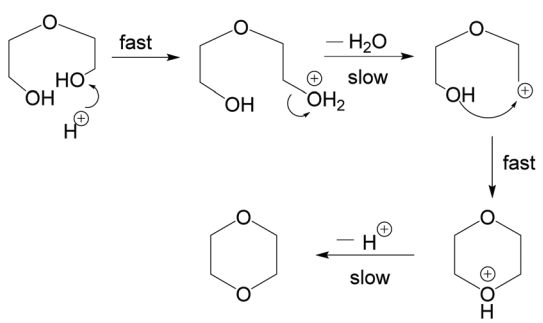
We have observed that a reagent combination of $NaIO_4$ and $NH_2OH{\cdot}HCl$ reacts with α,β-unsaturated ketones followed by the nucleophile ethylene glycol allowing the synthesis of 2,3-disubstituted 1,4-dioxanes using cesium carbonate as a base under Williamson ether synthesis. This reaction is useful for the synthesis of functionalized 1,4-dioxane having a carbonyl functionality. A variety of 2,3-disubstituted 1,4-dioxanes have been synthesized using these reaction conditions. A probable reaction mechanism has also been proposed.

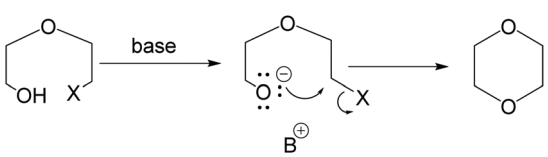
Introduction

In the literature, several methods have been reported for the synthesis of ethers, such as bimolecular dehydration,[1] Williamson ether synthesis[2] and Mitsunobu reaction.[3] In particular, for the cyclic ether synthesis, two common methodologies are used: (i) cyclo-dehydration of terminal diols[4] and (ii) Williamson ether synthesis *via* intramolecular S_N2 reaction of halogen-substituted alcohols. Cyclo-dehydration of terminal diols, such as 1,4-butanediol, 1,5-pentanediol and diethylene glycol, is a useful method to obtain oxygen heterocycles, such as tetrahydrofuran, tetrahydropyran and 1,4-dioxane, which are widely used as solvents in the chemical industry. In the cyclo-dehydration of diethylene glycol, 1,4-dioxane can be selectively obtained by the liquid-phase catalytic reaction in the presence of various catalysts such as sulfated zirconia,[5] alumina,[6] H-ZSM-5[7] or a Brønsted acidic ionic liquid (1-butyl-3-methylimidazolium hydrogen sulfate)[8] (Scheme 1). On the other hand, Williamson ether synthesis is a more reliable method (Scheme 2) and various reports are available in the literature such as reactions in the presence of methanol: a microwave absorber,[9] tetrabutylammonium bisulfate (TBAB): a phase transfer catalyst,[10] potassium hydride in paraffin: a base,[11] the salt of an aromatic or aliphatic carboxylic acid: a weak alkylating agent,[12] microwave irradiation using zinc as a catalyst,[13] and combinations of microwave and ultrasound.[14]

Besides using as a solvent, 1,4-dioxane scaffolds occur in a large number of natural products and bioactive compounds (Fig. 1).[15a,b,16] 1,4-Dioxane is used as a stabilizer in chlorinated solvents and is also used in a wide variety of industrial purposes. It is hydrophilic in nature. It is not susceptible to sorption to the soil rather retarded in groundwater. Very few methods have been reported in the literature[15] for the syn-



Scheme 1 1,4-Dioxane preparation *via* cyclo-dehydration reaction.



Scheme 2 1,4-Dioxane preparation *via* Williamson ether synthesis.

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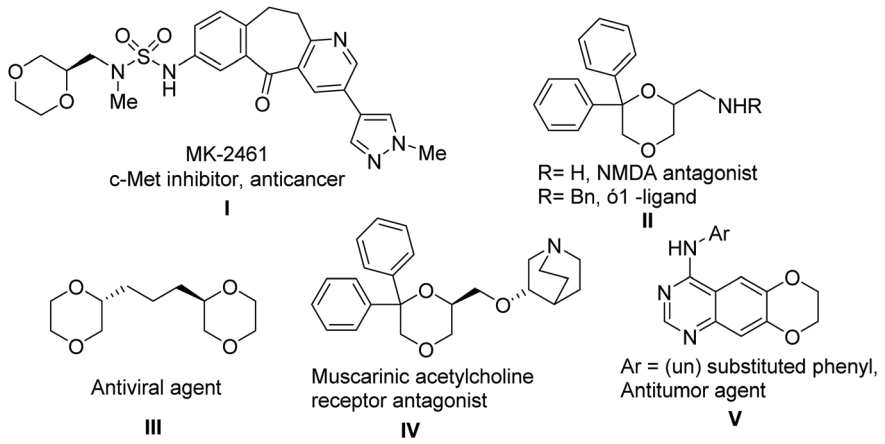


Fig. 1 1,4-Dioxane containing bio-active compounds.

thesis of substituted cyclic ethers, particularly 1,4-dioxane. Therefore, directly introducing the structure of a cyclic ether is an explorable and meaningful approach for the synthesis of the corresponding complex molecules.

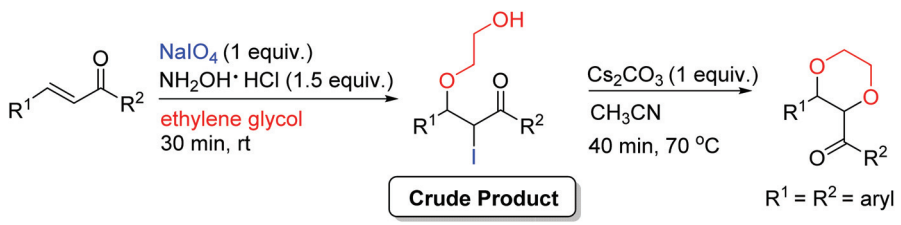
To synthesize polyether compounds such as dioxane systems, particularly 1,4-dioxane, the intramolecular version of these two strategies will not be useful as it is very difficult to control the formation of polymeric products. Again, under Williamson's conditions, it is very difficult to synthesize 1,4-dioxane derivatives, particularly those having the carbonyl functional group as it is more susceptible to the alkoxide giving different products under aldol reaction or other nucleophilic addition or elimination depending on the substrate. It is worth mentioning that carbonyl-containing compounds have much importance in various fields. To the best of our knowledge, only one such report is available in the literature to synthesize a substituted 1,4-dioxane with a carbonyl functionality adjacent to the dioxane ring.[17]

We are working to develop various organic reaction methodologies involving heterocyclic chemistry such as aziridine and azirine based on the current working practice.[18] We have observed that a reagent of $NaIO_4$ and $NH_2OH{\cdot}HCl$ is very effective for many organic transformations.[19] Here, we use the same reagent combination where α,β-unsaturated ketones can be converted into β-iodo-β′-hydroxy ethers using ethylene glycol as the nucleophile and reaction medium. This β-iodo-β′-hydroxy ether under Williamson ether synthesis can be easily converted to a 2,3-disubstituted 1,4-dioxane using cesium carbonate (Cs_2CO_3) as a base. It is worth mentioning that the product of the first step was isolated and the next step was carried out just by adding a base and solvent (Scheme 3). The carbonyl group of α,β-unsaturated ketones remained unaffected under these reaction conditions. A substituted 1,4-dioxane with a carbonyl group adjacent to the dioxane ring has been synthesized as the sole product.

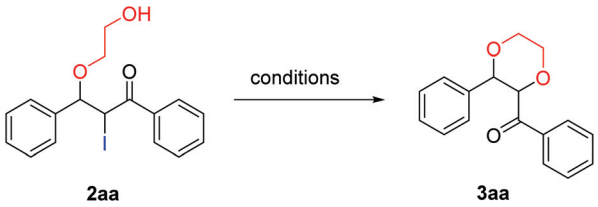
Results and discussion

The synthetic procedure involved two steps. In the first step, the reaction of a freshly prepared simple chalcone **1aa** with 1 equiv. $NaIO_4$ and 1.5 equiv. $NH_2OH{\cdot}HCl$ as an oxidant in ethylene glycol solvent at room temperature produced **2aa** in 90% isolated yield within 30 min at room temperature (Scheme 4). In the second step, 3-(2-hydroxyethoxy)-2-iodo-1,3-diphenylpropan-1-one (**2aa**) was allowed to react with a base Cs_2CO_3 in

Scheme 4 The 1st step: synthesis of 3-(2-hydroxyethoxy)-2-iodo-1,3-diphenylpropan-1-one (**2aa**).



Scheme 3 Synthesis of carbonyl-substituted 1,4-dioxane.



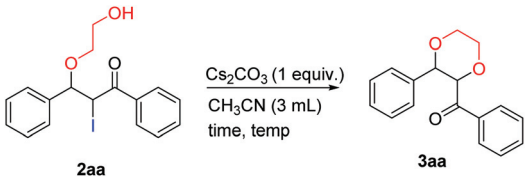
Scheme 5 The 2nd step: synthesis of carbonyl-substituted 1,4-dioxane (**3aa**).

CH_3CN solvent at 70 °C and the desired product **3aa** was isolated in 94% yield within 40 min (Scheme 5). Encouraged by this initial result, we carried out the reaction at different temperatures in different solvents to optimize the reaction conditions, and the results are shown in Tables 1 and 2. Here, it is worth mentioning that for the optimization of the reaction conditions, we have performed the second step with the crude product of the initial step.

At first, we tested the temperature effects of this reaction. It was found that at 70 °C temperature the reaction gave the best result (94% yield) after 40 min in acetonitrile solvent (Table 1). To examine the solvent effect, various common solvents such as acetonitrile, toluene, DCM, 1,2-DCE, acetone, DMF, DMSO, THF, 1,4-dioxane and methanol were tested (entries 1–10, Table 2). To our delight, a 94% yield of the desired product was obtained in acetonitrile (entry 1, Table 2). Then, a series of other bases such as K_2CO_3, Na_2CO_3, Ag_2CO_3, Li_2CO_3, NaOH and KOH was also investigated (entries 11–16, Table 2). The results indicated that other bases were not so effective in promoting the reaction, while Cs_2CO_3 gave a satisfactory yield of the product (entry 1, Table 2) and finally, these conditions have been accepted as optimized reaction conditions by using 1 equiv. Cs_2CO_3 in acetonitrile at 70 °C for 40 min (Table 2, entry 1). Increasing the amount of the base also could not increase the yield even after prolonged time (entry 17, Table 2).

After obtaining the optimized reaction conditions, we were interested in exploring the substrate scope of this methodology

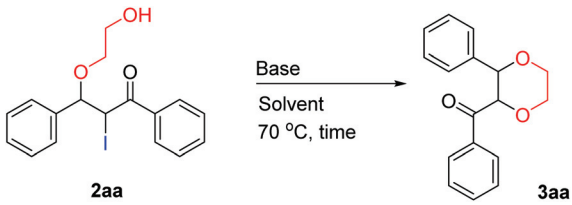
Table 1 Temperature effects on the synthesis of 1,4-dioxanes[a]



Entry	Temperature (°C)	Time	Yield (%)
1	rt	12 h	nd[b]
2	40	6 h	<10
3	55	1 h	70
4	70	40 min	94
5	100	40 min	90

[a] Reaction conditions: 1 mmol of **2aa** was reacted with Cs_2CO_3 (1 equiv.) in acetonitrile solvent (3 mL) at various temperatures with different reaction times. [b] Not detected in TLC.

Table 2 Optimization of the reaction conditions[a]

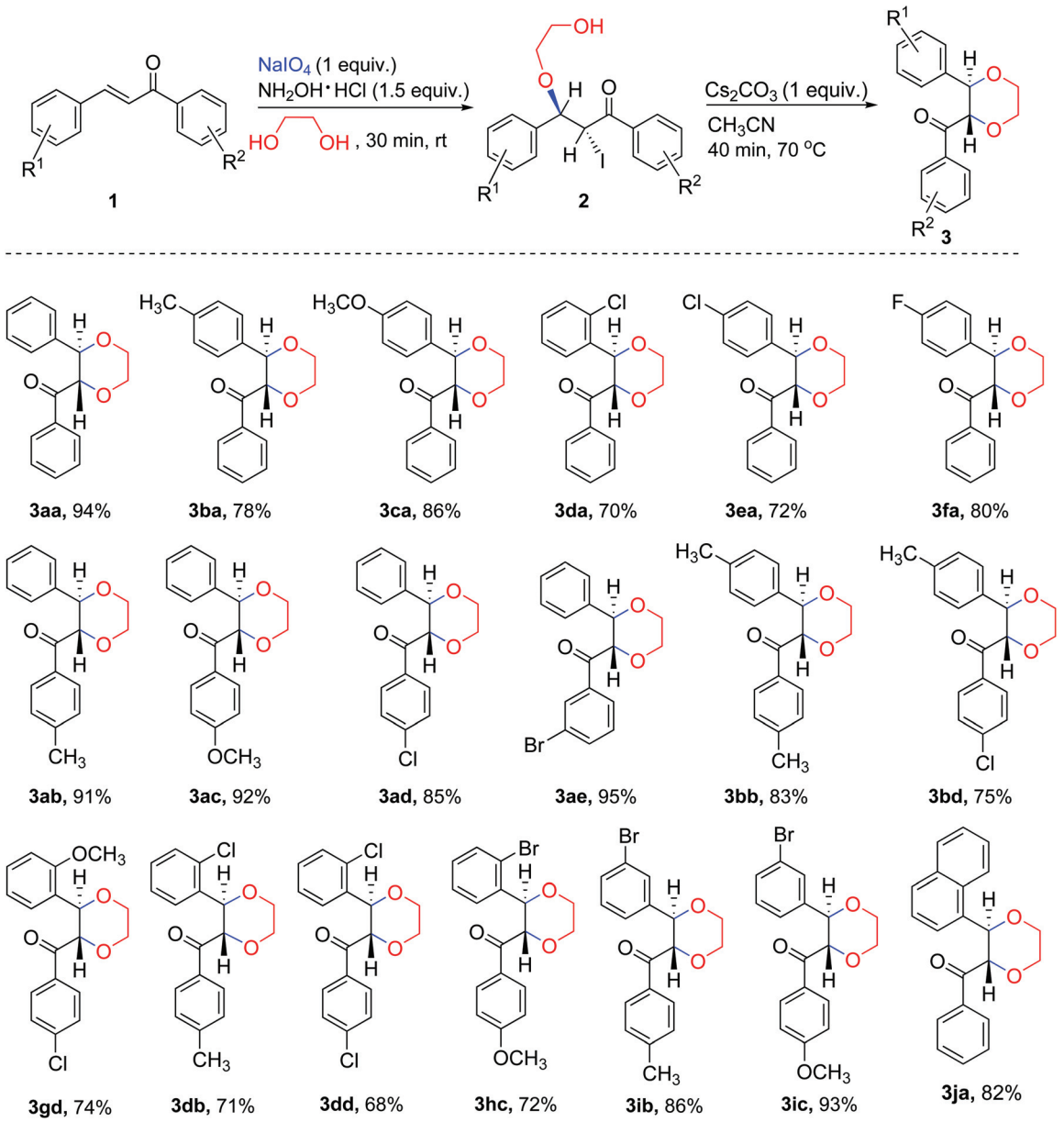


Entry	Base (equiv.)	Solvent	Time (min)	Yield (%)
1	Cs_2CO_3 (1)	CH_3CN	40	94
2	Cs_2CO_3 (1)	Toluene	40	55
3	Cs_2CO_3 (1)	DCM	40	nd[b]
4	Cs_2CO_3 (1)	1,2-DCE	40	35
5	Cs_2CO_3 (1)	Acetone	40	73
6	Cs_2CO_3 (1)	DMF	40	88
7	Cs_2CO_3 (1)	DMSO	40	Trace
8	Cs_2CO_3 (1)	THF	40	47
9	Cs_2CO_3 (1)	1,4-Dioxane	40	30
10	Cs_2CO_3 (1)	MeOH	40	32
11	K_2CO_3 (1)	CH_3CN	40	nd[b]
12	Na_2CO_3 (1)	CH_3CN	40	nd[b]
13	Ag_2CO_3 (1)	CH_3CN	40	nd[b]
14	Li_2CO_3 (1)	CH_3CN	40	nd[b]
15	NaOH (1)	CH_3CN	40	nd[b]
16	KOH (1)	CH_3CN	40	nd[b]
17	Cs_2CO_3 (1.5)	CH_3CN	60	85

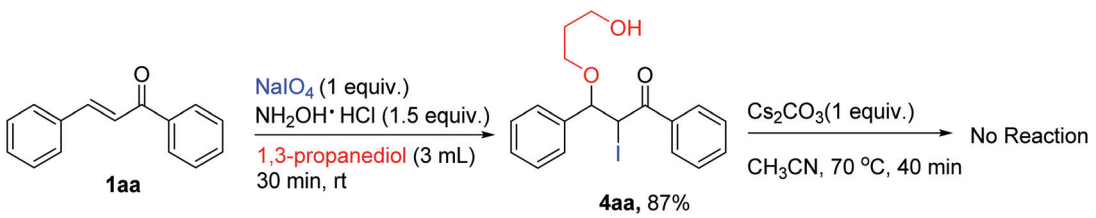
[a] Reaction conditions: 1 mmol of **2aa** was reacted at 70 °C with various bases in various solvents. [b] Not detected in TLC.

and the results are presented in Scheme 6. A series of substituted 1,4-dioxanes were synthesized under the optimized reaction conditions in good to excellent yields (**3aa–3ic**). It was observed that the α,β-unsaturated ketones substituted with electron-donating substituents such as –Me (**1ba**) and –OMe (**1ca**) as well as electron-withdrawing groups such as –chloro (**1da** & **1ea**) and –fluoro (**1fa**) groups reacted easily to afford the desired products (**3ba–3ea**) in good yields. α,β-Unsaturated ketones in which the ketone part was substituted with electron-donating substituents such as –Me (**1ab**) and –OMe (**1ac**) provided the corresponding products **3ab** and **3ac** in 91% and 92% yields, respectively, while the reactions with electron-withdrawing groups such as –Cl (**1ad**) and –Br (**1ae**) afforded the desired products **3ad** and **3ae** in 85% and 95% yields, respectively. Substitution in the phenyl rings from both sides of the α,β-unsaturated ketones was tested and a similar reaction affording the desired products was observed. Moderate to high yields were observed (68–93%) for all the cases bearing both electron-withdrawing and electron-donating functional groups (**3bb–3ic**). In addition, 1-naphthaldehyde substituted α,β-unsaturated ketone, namely, 3-(naphthalen-1-yl)-1-phenylprop-2-en-1-one (**1ja**), also reacted smoothly under these conditions to afford the product (3-(naphthalen-1-yl)-1,4-dioxan-2-yl)(phenyl)methanone (**3ja**) in 82% yield.

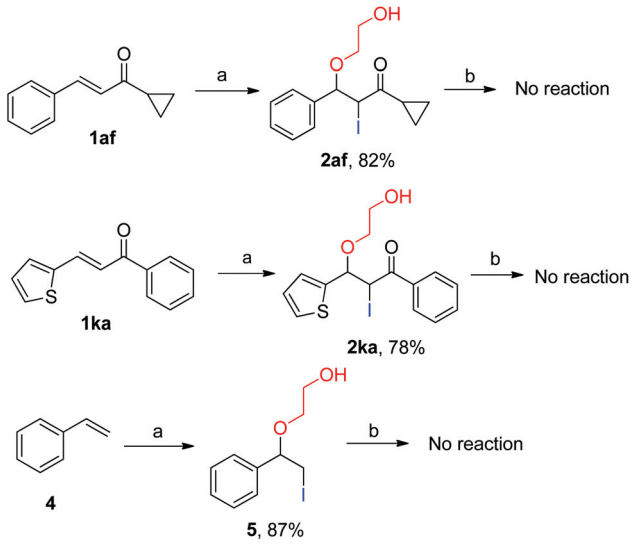
However, we were unable to synthesize large ring dioxanes. In an attempt to achieve the synthesis, we carried out a reaction taking 1,3-propanediol instead of ethylene glycol in the initial step and obtained 3-(3-hydroxypropoxy)-2-iodo-1,3-



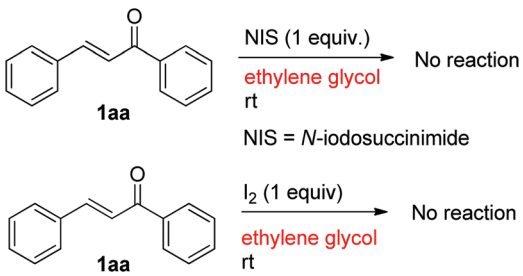
Scheme 6 Substrate scope of the present method. Reaction conditions: For the 1st step: **1** (1 mmol), $NaIO_4$ (1 mmol) and $NH_2OH{\cdot}HCl$ (1.5 mmol) in 3 mL of ethylene glycol at room temperature for 30 min. For the 2nd step: **2** (1 mmol) and Cs_2CO_3 (1 mmol) in CH_3CN solvent (3 mL) at 70 °C for 40 min.



Scheme 7 Additional experiment: attempt to synthesize a large ring dioxane.



Scheme 8 Studies with other chalocones having aliphatic and heterocyclic moieties as well as with styrene.



Scheme 9 Control experiments with other iodine sources.

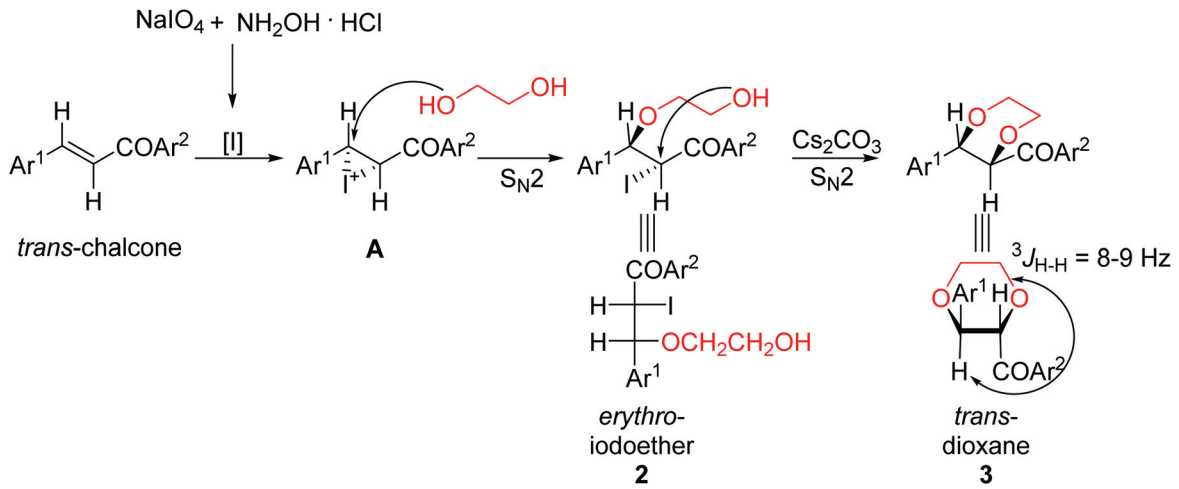
diphenylpropan-1-one (**4aa**) in 87% yield in the 1st step (Scheme 7). However, **4aa** remained unreacted with cesium carbonate.

Again, it is worth mentioning that chalcones having aliphatic and heterocyclic moieties did not respond to afford the desired products. After the reaction under similar conditions we isolated only the β-iodo-β′-hydroxy ethers which are products formed before cyclization (**2af** & **2ka**) in 82% and 78% yields, respectively. Similarly, simple styrene also underwent the 1st step but not the desired cyclization step (Scheme 8).

Finally, we carried out two control experiments to understand the mechanistic pathway of the reaction. When the reaction was carried out in the presence of *N*-iodosuccinimide (NIS) and simple molecular iodine under similar reaction conditions no product was obtained even in the 1st step (Scheme 9).

Thus, a probable mechanism has been proposed for this two-step conversion (Scheme 10). Based on the present experiments, the literature[17,20] and our previous works[19] on the preparation of iodohydrine compounds it can be suggested that an *in situ* generated electrophilic iodine reagent undergoes simple addition to the chalcone giving the intermediate [**A**]. In the presence of excess ethylene glycol which acts as a nucleophile and reacts with the intermediate [**A**] giving the compound **2**. Then in the presence of a base, the intramolecular Williamson ether synthesis, probably *via* the S_N2 mechanistic pathway, produces the desired product **3**.

We should especially mention the intriguing stereoselectivity of the proposed method. Dioxanes **3** are formed as a single *trans*-stereoisomer as established by the spin–spin coupling constant (SSCC) between protons at C2 and C3 of the dioxane ring. Our structural assignment is based on the fact that *trans*-substituted dioxanes typically exhibit a SSCC of 9 Hz, while *cis*-substituted counterparts exhibit a 4 Hz SSCC.[21] The observed value of 8–9 Hz is consistent with the *trans*-configuration of substituents at positions C2 and C3 (please see the ESI† also). Thus, in the ^{1}H NMR spectrum of dioxanes **3**,



Scheme 10 Proposed reaction mechanism.

the characteristic signals of protons at C2 and C3 are registered as doublets with vicinal SSCC 8–9 Hz at 4.8–4.9 ppm. The remaining dioxane ring protons (at C5 and C6 carbon atoms) and aromatic protons were registered as multiplets at 4.0 and 6.7–7.7 ppm, respectively. In the ^{13}C NMR spectrum, all expected signals are observed as: atoms C2 and C3 at 80 ppm and atoms C5 and C6 at 66 ppm; a carbonyl atom at 195 ppm and aryl carbons in the range 127 to 160 ppm.

The high stereoselectivity of the proposed method was attributed to the *trans*-configuration of the starting chalcone and selectivity of the following transformations: iodination of the *trans*-chalcone gives *trans*-iodonium cyclic cation **A**, and the ring opening of this cyclic iodonium intermediate with ethylene glycol yields *erythro*-iodoether **2** followed by configuration inversion during the S_N2 substitution of iodine forming the dioxane ring (Scheme 10).

Conclusions

Alkoxide is very useful in organic synthesis acting as a nucleophile and a base depending on the reaction conditions. Synthesis of ethers following this concept has been well studied in organic chemistry and it is one of the best strategies known as Williamson ether synthesis. This reaction can be useful in intermolecular and intramolecular ways for the preparation of simple and mixed ethers for acyclic systems and cyclic systems. But the synthesis of functionalized 1,4-dioxanes is very limited under these conditions, particularly the carbonyl functional group as it is more susceptible to the alkoxide giving different products under aldol reaction or other nucleophilic addition or elimination depending on the substrate. We have shown that using the reagent combination of $NaIO_4$ and $NH_2OH{\cdot}HCl$ an α,β-unsaturated ketone can be converted into a β-iodo-β′-hydroxy ether using the nucleophile ethylene glycol which allows the synthesis of a substituted 1,4-dioxane with a carbonyl functionality adjacent to the dioxane ring under Williamson ether synthesis using cesium carbonate as a base. During the reaction, the *trans*-configuration of the substituents at the double bond was preserved and, as a consequence, the formation of a single diastereomeric dioxane was observed.

Experimental section

General information

All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer with solutions in $CDCl_3$. Chemical shifts are expressed in parts per million (δ), the signals are reported as s (singlet), d (doublet), t (triplet), m (multiplet), and dd (doublet of doublets), and coupling constants (J) are given in Hz. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ solution. TLC was performed on silica gel coated glass slides. Silica gel (60–120 mesh) was used for column chromatography. Petroleum ether refers to the fraction boiling in a range of 60–80 °C unless otherwise mentioned. Melting points were determined on a glass disk with an electric hot plate. All solvents were dried and distilled before use. Commercially available substrates were freshly distilled before the reaction. All reactions involving moisture-sensitive reactants were executed using oven-dried glassware. All the α,β-unsaturated ketones were prepared according to a previously reported method.[22]

Typical procedure for the synthesis of compounds 3

The synthetic procedure involved two steps. In the first step, α,β-unsaturated ketone **1** (1 mmol), sodium periodate (1 mmol) and hydroxylamine hydrochloride (1.5 mmol) were taken with ethylene glycol solvent (3 mL) in a sealed tube. The reaction mixture was stirred for 30 min at room temperature. After completion (TLC) the reaction mixture was diluted with a 1 : 1 mixture of water/ethyl acetate (10 mL, v/v) followed by washing with brine solution (1 × 10 mL) and sodium thiosulfate solution (1 × 10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. After the evaporation of the solvent the crude product was obtained.

In the second step, the crude product was dissolved in acetonitrile solvent (3 mL) and cesium carbonate (1 equiv.) was added to that solution. The reaction mixture was stirred for 40 min at 70 °C. After completion (TLC) the reaction mixture was diluted with a 1 : 1 mixture of water/ethyl acetate (10 mL, v/v) followed by washing with brine solution (1 × 10 mL). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent furnished the crude product which was subjected to column chromatography using ethyl acetate–petroleum ether as the eluent to obtain the analytically pure product.

3-(2-Hydroxyethoxy)-2-iodo-1-phenyl-3-(*p*-tolyl)propan-1-one (2ba). Colourless liquid, R_f = 0.60 (petroleum ether/EtOAc = 80/20); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05–8.03 (m, 2H), 7.61–7.58 (m, 1H), 7.50–7.47 (m, 2H), 7.34 (m, J = 8.0 Hz, 2H), 7.22 (m, J = 8.0 Hz, 2H), 5.41 (m, J = 10.0 Hz, 1H), 5.09 (m, J = 10.0 Hz, 1H), 3.63–3.40 (m, 4H), 2.39 (s, 3H). Anal. Calcd for $C_{18}H_{19}IO_3$: C, 52.70; H, 4.67%; Found: C, 52.76; H, 4.70%.

1-(4-Chlorophenyl)-3-(2-hydroxyethoxy)-2-iodo-3-(*p*-tolyl)propan-1-one (2bd). Colourless liquid, R_f = 0.60 (petroleum ether/EtOAc = 80/20); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00–7.95 (m, 2H), 7.48–7.45 (m, 2H), 7.35–7.33 (m, 2H), 7.26–7.22 (m, 2H), 5.35 (m, J = 10.0 Hz, 1H), 5.07 (m, J = 10.0 Hz, 1H), 3.62–3.41 (m, 4H), 2.39 (s, 3H). Anal. Calcd for $C_{18}H_{18}ClIO_3$: C, 48.62; H, 4.08%; Found: C, 48.68; H, 4.15%.

Phenyl(3-phenyl-1,4-dioxan-2-yl)methanone (3aa). Off-white gum (252 mg, yield 94%); R_f = 0.50 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70–7.67 (m, 2H), 7.43–7.39 (m, 1H), 7.31–7.23 (m, 4H), 7.18–7.11 (m, 3H), 4.88 (d, J = 8.8 Hz, 1H), 4.81 (d, J = 8.8 Hz, 1H), 4.02–3.95 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.4, 137.1, 135.9, 133.4, 128.8, 128.6, 128.4, 127.6, 81.1, 79.9, 66.75, 66.68. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01%; Found: C, 76.06; H, 6.05%.

Phenyl(3-(*p*-tolyl)-1,4-dioxan-2-yl)methanone (3ba). Yellow liquid (220 mg, yield 78%); R_f = 0.60 (petroleum ether/EtOAc =

91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74–7.72 (m, 2H), 7.47–7.43 (m, 1H), 7.32–7.28 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 4.89–4.79 (m, 2H), 4.04–3.98 (m, 4H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.5, 138.3, 135.9, 134.1, 133.4, 129.1, 128.9, 128.4, 127.5, 81.2, 79.8, 66.8, 66.7, 21.2. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%; Found: C, 76.51; H, 6.38%.

(3-(4-Methoxyphenyl)-1,4-dioxan-2-yl)(phenyl)methanone (3ca). Yellow liquid (256 mg, yield 86%); R_f = 0.50 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67–7.65 (m, 2H), 7.40–7.36 (m, 1H), 7.25–7.15 (m, 4H), 6.66–6.63 (m, 2H), 4.80 (d, J = 8.8 Hz, 1H), 4.71 (d, J = 9.2 Hz, 1H), 3.95–3.90 (m, 4H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.6, 159.7, 135.8, 133.4, 129.3, 128.9, 128.4, 113.8, 81.1, 79.4, 66.8, 66.7, 55.3. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%; Found: C, 72.40; H, 6.02%.

(3-(2-Chlorophenyl)-1,4-dioxan-2-yl)(phenyl)methanone (3da). Orange gum (212 mg, yield 70%); R_f = 0.55 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72–7.70 (m, 2H), 7.58–7.56 (m, 1H), 7.42–7.38 (m, 1H), 7.26–7.21 (m, 3H), 7.08–7.04 (m, 2H), 5.22 (d, J = 8.8 Hz, 1H), 4.99 (d, J = 8.4 Hz, 1H), 4.09–4.02 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 135.7, 135.1, 133.4, 133.3, 129.7, 129.6, 128.94, 128.89, 128.1, 127.0, 82.2, 76.3, 66.9, 66.7. Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99%; Found: C, 67.39; H, 5.04%.

(3-(4-Chlorophenyl)-1,4-dioxan-2-yl)(phenyl)methanone (3ea). Yellow liquid, 218 mg (yield 72%); R_f = 0.60 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75–7.73 (m, 2H), 7.50–7.46 (m, 1H), 7.35–7.31 (m, 2H), 7.28–7.25 (m, 2H), 7.18–7.15 (m, 2H), 4.85–4.80 (m, 2H), 4.03–3.98 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.1, 135.8, 135.7, 134.3, 133.7, 129.1, 128.9, 128.6, 127.5, 81.0, 79.0, 66.8. Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99%; Found: C, 67.41; H, 4.95%.

(3-(4-Fluorophenyl)-1,4-dioxan-2-yl)(phenyl)methanone (3fa). Yellow liquid (229 mg, yield 80%); R_f = 0.45 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74–7.72 (m, 2H), 7.49–7.46 (m, 1H), 7.34–7.29 (m, 4H), 6.91–6.86 (m, 2H), 4.87–4.81 (m, 2H), 4.05–3.99 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.3, 162.7 (d, $^1J_{C-F}$ = 244 Hz), 135.7, 133.7, 133.1, 129.4 (d, $^4J_{C-F}$ = 8 Hz), 128.7 (d, $^3J_{C-F}$ = 30 Hz), 115.4 (d, $^2J_{C-F}$ = 22 Hz), 81.1, 79.2, 66.9, 66.7. Anal. Calcd for $C_{17}H_{15}FO_3$: C, 71.32; H, 5.28%; Found: C, 71.27; H, 5.25%.

(3-Phenyl-1,4-dioxan-2-yl)(*p*-tolyl)methanone (3ab). Off-white gum (257 mg, yield 91%); R_f = 0.50 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, J = 8.4 Hz, 2H), 7.33–7.30 (m, 2H), 7.22–7.15 (m, 3H), 7.09 (d, J = 8.0 Hz, 2H), 4.90–4.83 (m, 2H), 4.04–3.98 (m, 4H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 144.4, 137.2, 133.4, 129.2, 129.0, 128.5, 128.4, 127.6, 81.0, 80.0, 66.8, 66.7, 21.8. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43%; Found: C, 76.51; H, 6.38%.

(4-Methoxyphenyl)(3-phenyl-1,4-dioxan-2-yl)methanone (3ac). Yellow gum (274 mg, yield 92%); R_f = 0.60 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72–7.69 (m, 2H), 7.33–7.30 (m, 2H), 7.22–7.15 (m, 3H), 6.77–6.75 (m, 2H), 4.87–4.82 (m, 2H), 4.05–3.97 (m, 4H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.7, 163.8, 137.2, 131.2, 128.9, 128.5, 128.4, 127.6, 113.7, 81.0, 80.0, 66.8, 66.7, 55.5. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08%; Found: C, 72.41; H, 6.02%.

(4-Chlorophenyl)(3-phenyl-1,4-dioxan-2-yl)methanone (3ad). Yellow liquid (257 mg, yield 85%); R_f = 0.45 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65–7.63 (m, 2H), 7.31–7.25 (m, 4H), 7.23–7.16 (m, 3H), 4.86–4.78 (m, 2H), 4.05–3.97 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.4, 140.0, 136.9, 134.1, 130.2, 128.8, 128.5, 127.6, 81.3, 80.0, 66.8, 66.7. Anal. Calcd for $C_{17}H_{15}ClO_3$: C, 67.44; H, 4.99%; Found: C, 67.40; H, 4.92%.

(3-Bromophenyl)(3-phenyl-1,4-dioxan-2-yl)methanone (3ae). Yellow liquid (330 mg, yield 95%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70–7.69 (m, 1H), 7.55–7.53 (m, 1H), 7.48–7.45 (m, 1H), 7.23–7.21 (m, 2H), 7.14–7.05 (m, 4H), 4.76 (d, J = 8.8 Hz, 1H), 4.70 (d, J = 8.8 Hz, 1H), 3.96–3.92 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.2, 137.5, 136.8, 136.2, 131.7, 129.9, 128.8, 128.5, 127.5, 127.2, 122.7, 81.3, 79.9, 66.7, 66.6. Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.35%; Found: C, 58.75; H, 4.29%.

***p*-Tolyl(3-(*p*-tolyl)-1,4-dioxan-2-yl)methanone (3bb).** Yellow gum (246 mg, yield 83%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 4.86–4.80 (m, 2H), 4.02–3.97 (m, 4H), 2.33 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.0, 144.3, 138.2, 134.2, 133.5, 129.12, 129.07, 129.0, 127.5, 81.1, 79.7, 66.8, 66.7, 21.7, 21.2. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.08%; Found: C, 76.95; H, 6.01%.

(4-Chlorophenyl)(3-(*p*-tolyl)-1,4-dioxan-2-yl)methanone (3bd). Yellow liquid (237 mg, yield 75%); R_f = 0.60 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61–7.57 (m, 2H), 7.22–7.19 (m, 3H), 7.10 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 7.6 Hz, 2H), 4.76–4.68 (m, 2H), 3.97–3.92 (m, 4H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.3, 139.8, 138.4, 134.1, 133.8, 130.2, 129.1, 128.6, 127.3, 81.3, 79.7, 66.7, 66.6, 21.1. Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41%; Found: C, 68.20; H, 5.35%.

(4-Chlorophenyl)(3-(2-methoxyphenyl)-1,4-dioxan-2-yl)methanone (3gd). Yellow gum (246 mg, yield 74%); R_f = 0.50 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61–7.59 (m, 2H), 7.55–7.52 (m, 1H), 7.20–7.18 (m, 2H), 7.12–7.10 (m, 1H), 6.96–6.93 (m, 1H), 6.42 (d, J = 8.0 Hz, 1H), 5.10 (d, J = 8.8 Hz, 1H), 4.78 (d, J = 8.4 Hz, 1H), 4.08–4.03 (m, 3H), 3.97–3.92 (m, 1H), 3.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 155.8, 139.3, 134.2, 130.0, 129.6, 128.2, 127.4, 125.6, 120.9, 109.9, 84.0, 74.5, 67.1, 66.7, 54.5. Anal. Calcd for $C_{18}H_{17}ClO_4$: C, 64.97; H, 5.15%; Found: C, 65.02; H, 5.11%.

(3-(2-Chlorophenyl)-1,4-dioxan-2-yl)(*p*-tolyl)methanone (3db). Orange gum (225 mg, yield 71%); R_f = 0.50 (petroleum ether/EtOAc = 94/6); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.62 (m, 2H), 7.59–7.56 (m, 1H), 7.23–7.21 (m, 1H), 7.08–7.04 (m, 4H), 5.23 (d, J = 8.8 Hz, 1H), 4.97 (d, J = 8.4 Hz, 1H), 4.09–3.98 (m, 4H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.6, 144.2, 135.2, 133.5, 133.2, 129.7, 129.6, 129.1, 129.0, 128.9, 127.0, 82.1, 76.4,

66.9, 66.7, 21.7. Anal. Calcd for $C_{18}H_{17}ClO_3$: C, 68.25; H, 5.41%; Found: C, 68.20; H, 5.46%.

(4-Chlorophenyl)(3-(2-chlorophenyl)-1,4-dioxan-2-yl)methanone (3dd). Yellow liquid (229 mg, yield 68%); R_f = 0.45 (petroleum ether/EtOAc = 90/10); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.66 (m, 2H), 7.60–7.58 (m, 1H), 7.25–7.18 (m, 3H), 7.13–7.05 (m, 2H), 5.20 (d, J = 8.8 Hz, 1H), 4.91 (d, J = 8.8 Hz, 1H), 4.10–3.99 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.9, 139.8, 135.0, 133.9, 133.3, 130.3, 129.8, 129.6, 128.9, 128.5, 127.2, 82.7, 76.3, 66.9, 66.7. Anal. Calcd for $C_{17}H_{14}Cl_2O_3$: C, 60.55; H, 4.19%; Found: C, 60.60; H, 4.12%.

(3-(2-Bromophenyl)-1,4-dioxan-2-yl)(4-methoxyphenyl)methanone (3hc). Yellow liquid (272 mg, yield 72%); R_f = 0.50 (petroleum ether/EtOAc = 91/9); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75–7.72 (m, 2H), 7.58–7.55 (m, 1H), 7.29–7.26 (m, 2H), 7.03–6.99 (m, 1H), 6.74–6.71 (m, 2H), 5.22–5.20 (m, 1H), 4.96–4.94 (m, 1H), 4.09–3.98 (m, 4H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.3, 163.6, 136.9, 133.0, 131.4, 129.9, 129.2, 128.7, 127.6, 123.8, 113.4, 82.1, 78.5, 66.9, 66.7, 55.5. Anal. Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54%; Found: C, 57.25; H, 4.59%.

(3-(3-Bromophenyl)-1,4-dioxan-2-yl)(*p*-tolyl)methanone (3ib). Yellow liquid (311 mg, yield 86%); R_f = 0.55 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73–7.72 (m, 1H), 7.66–7.64 (m, 1H), 7.57–7.54 (m, 1H), 7.19–7.15 (m, 3H), 7.02–7.00 (m, 2H), 4.81 (d, J = 8.8 Hz, 1H), 4.73 (d, J = 8.8 Hz, 1H), 4.01–3.99 (m, 4H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.4, 138.6, 137.6, 136.1, 133.9, 131.8, 129.9, 129.2, 127.4, 127.3, 122.7, 81.6, 79.8, 66.8, 66.7, 21.2. Anal. Calcd for $C_{18}H_{17}BrO_3$: C, 59.85; H, 4.74%; Found: C, 59.93; H, 4.69%.

(3-(3-Bromophenyl)-1,4-dioxan-2-yl)(4-methoxyphenyl)methanone (3ic). Yellow liquid (351 mg, yield 93%); R_f = 0.60 (petroleum ether/EtOAc = 93/7); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75–7.74 (m, 1H), 7.65–7.62 (m, 1H), 7.55–7.52 (m, 1H), 7.21–7.13 (m, 3H), 6.73–6.71 (m, 2H), 4.79 (d, J = 8.8 Hz, 1H), 4.70 (d, J = 9.2 Hz, 1H), 3.98–3.97 (m, 4H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 194.3, 159.8, 137.5, 136.0, 131.7, 129.9, 129.0, 128.7, 127.2, 122.6, 113.8, 81.4, 79.4, 66.7, 66.6, 55.2. Anal. Calcd for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54%; Found: C, 57.25; H, 4.50%.

(3-(Naphthalen-1-yl)-1,4-dioxan-2-yl)(phenyl)methanone (3ja). Yellow liquid (261 mg, yield 82%); R_f = 0.50 (petroleum ether/EtOAc = 92/8); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, J = 8.8 Hz, 1H), 7.66–7.58 (m, 3H), 7.50–7.45 (m, 1H), 7.42–7.36 (m, 3H), 7.33–7.29 (m, 1H), 7.25–7.21 (m, 1H), 7.04–7.00 (m, 2H), 5.48 (d, J = 8.4 Hz, 1H) 5.33 (d, J = 8.4 Hz, 1H), 4.18–4.09 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.0, 135.6, 133.7, 133.1, 131.0, 129.3, 128.7, 128.2, 127.8, 126.4, 125.9, 125.6, 125.1, 123.7, 81.1, 67.2, 66.8. Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70%; Found: C, 79.15; H, 5.76%.

Conflicts of interest

There are no conflicts to declare.

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