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Ti(IV)-catalyzed cascade synthesis of tetrahydrofuro[3,2-*d*]oxazole from arene-1,4-diones†

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A tetrahydrofuro[3,2-*d*]oxazole scaffold was synthesized efficiently and stereoselectively. The tandem ionic hydrogenation, ketalization, and intramolecular cyclization of arene-1,4-diones with a combination of $TiCl_4$/Et_3SiH give facile access to tetrahydrofuro-[3,2-*d*]oxazole derivatives in good yields at room temperature.

Fused bicyclic oxygen-containing heterocycles are embodied in a wide range of natural products, modified sugar derivatives, and important bioactive molecules.[1] Among these heterocycles, the tetrahydrofuro[3,2-*d*]oxazole motif has been exploited as a versatile biomimetic synthetic precursor for the chemical syntheses of some rare sugars and antisense oligonucleotides.[2,3] It is reported that important groups of compounds with the tetrahydrofuro[3,2-*d*]oxazole skeleton are prodrugs of caspase inhibitors with apoptosis-regulating activity (Fig. 1).[4] However, there are very limited methods available to stereoselectively synthesize such scaffolds.[5] Most methodologies for the construction of this type of heterocycles were from D-glucosamine. Therefore, the search for new synthetic strategies leading to these scaffolds from simple starting materials in a sustainable and atom-economical fashion is of continued interest of our group.

Recently, we developed a mild and efficient method for the synthesis of tetralins *via* sequential ionic hydrogenation and cyclization in the presence of $TiCl_4$ and Et_3SiH from the substituted phenylpentane-1,4-dione substrates.[6] We believe that the same concept can be applied to the synthesis of other heterocycles. However, when NHAc and COOEt were incorporated into the C(3) position of 1-(4-phenoxyphenyl)pentane-1,4-dione (**3**), the treatment of substrate **1k** with titanium chloride and triethylsilane only afforded tetrahydrofuro[3,2-*d*]oxazole racemate **2k**, instead of the attempted product **5** (Scheme 1).

We did not find any other diastereomers except one pair of enantiomers indicated as **2k**. In order to confirm the relative configuration, molecule **2k** was converted into **6** which is a solid by $NaBH_4$/K_2HPO_4 reduction (Scheme 2). The configur-

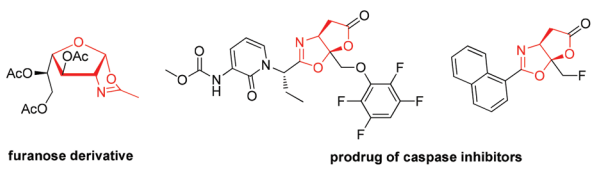
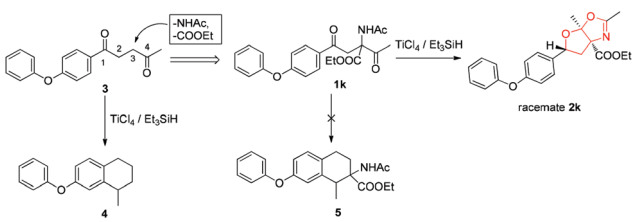
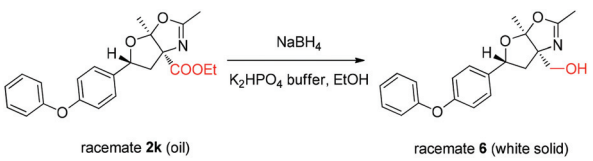


Fig. 1 Representative examples of tetrahydrofuro[3,2-*d*]oxazole derivatives.



Scheme 1 Strategy for the synthesis of tetrahydrofuro[3,2-*d*]oxazole derivatives.



Scheme 2 Reduction of **2k** in the presence of $NaBH_4$/K_2HPO_4 buffer.

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†Electronic supplementary information (ESI) available: Experimental details, compound characterization data and X-ray crystal structure data (CIF) for compound **6**. CCDC 978589. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob00174a

ation of the tetrahydrofuro[3,2-*d*]oxazole motif was confirmed by an X-ray crystal structure of **6** (CCDC 978589, Fig. 2). The X-ray analysis data demonstrate the exclusive formation of *cis*-fused bicycles. The ring conjunction methyl and hydroxymethyl substituents were *syn*, as expected, and they were *anti* to the benzyl hydrogen. So we can draw the conclusion that compound **2k** also has the same relative configuration. This interesting result encouraged us to explore the conditions, scope and mechanism of this novel reaction.

We initiated our studies by choosing **1k** as the model substrate. First, we screened various Lewis acids, Brønsted acids, and solvents that might promote the heterocyclization. The results indicated that only $TiCl_4$ could promote the reaction to give racemate **2k**. The choice of solvents was also crucial for the reaction. The use of 1,2-dichloroethane resulted in a moderate yield of products (Table 1, entry 7) and toluene gave a much lower yield (Table 1, entry 8). Dichloromethane was proved to be a good solvent for this reaction (Table 1, entry 4). To further optimize the reaction parameters, the combination of catalyst and reducing agent loading was screened. It was found that the increased ratio of $TiCl_4$ to Et_3SiH resulted in higher yields of the product (Table 1, entries 1–4) while more than one equivalent of Et_3SiH decreased the yield presumably due to the over reduction of other functional groups (Table 1, entries 4–6).

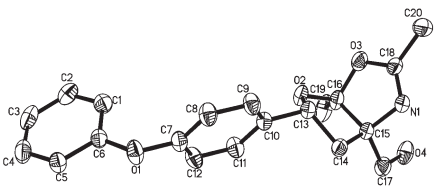
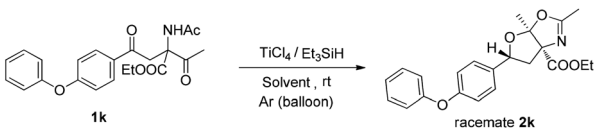


Fig. 2 X-ray crystal structure of **6**.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (equiv.)	Reductant (equiv.)	Solvent	Yield[b] (%)
1	$TiCl_4$ (1.1)	Et_3SiH (1.1)	CH_2Cl_2	NR[c]
2	$TiCl_4$ (2.1)	Et_3SiH (1.1)	CH_2Cl_2	65
3	$TiCl_4$ (3.1)	Et_3SiH (1.1)	CH_2Cl_2	74
4	$TiCl_4$ (3.8)	Et_3SiH (1.1)	CH_2Cl_2	81
5	$TiCl_4$ (3.8)	Et_3SiH (2.1)	CH_2Cl_2	52
6	$TiCl_4$ (3.8)	Et_3SiH (3.8)	CH_2Cl_2	45
7	$TiCl_4$ (3.8)	Et_3SiH (1.1)	$ClCH_2CH_2Cl$	68
8	$TiCl_4$ (3.8)	Et_3SiH (1.1)	Toluene	15
9	$TiCl_4$ (3.8)	Et_3SiH (1.1)	CH_3CN	NR
10	$TiCl_4$ (3.8)	Et_3SiH (1.1)	THF	NR

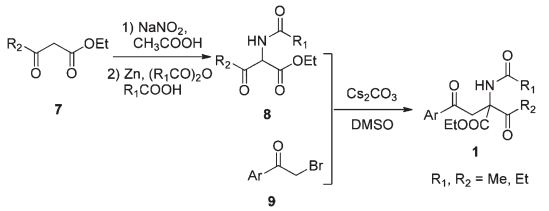
[a] All reactions were performed at room temperature under an argon atmosphere for 4 h with 0.5 mmol of **1k**, the indicated amount of $TiCl_4$ and Et_3SiH in 5.0 mL of the indicated solvent. [b] Isolated yields. [c] No reaction.

Encouraged by this promising result, a series of arene-1,4-dione substrates, prepared by the method described in Scheme 3, were used to investigate the scope of the method for tetrahydrofuro[3,2-*d*]oxazole skeleton formation. Intermediate **8** was prepared from ethyl acetoacetate/propionylacetate **7** *via* nitrosation, reduction and acylation. However, the reaction of aroylation did not occur when R_1 groups were aryl or aromatic heterocyclic substituents. Subsequent replacement of the bromide group of **9** with **8** gave substrate **1**.

To our delight, the arene-1,4-dione substrate **1** smoothly underwent heterocyclization to afford tetrahydrofuro[3,2-*d*]-oxazole racemate **2** in good yields and a series of functional groups including fluoro, chloro, bromo, methoxyl, trifluoromethyl, and phenoxyl on the aryl ring were well tolerated under the optimal reaction conditions (**2a–2t** in Table 2). It was noticed that the substrates containing electron-donating groups, such as alkyl, methoxy, and phenoxy, in general gave higher yields (**2b–2d**, **2h**, **2k–2o**, **2q–2t**), while electron deficient substrates with trifluoromethyl and halogen substituents gave lower yields (**2e–2g**, **2i**). Moreover, heterocyclic substrates could also react with $TiCl_4$ and Et_3SiH to smoothly afford the expected products in good yields (**2j**, **2p**). However, for substrates bearing strong electron-withdrawing groups, such as nitro, cyano, and pyridyl, no reaction occurred in the presence of $TiCl_4$ and Et_3SiH under the optimized conditions. Furthermore, we examined the heterocyclization of arene-1,4-dione containing substitutions on alkyl counterparts ($\mathbf{R_1}$, $\mathbf{R_2}$). Various substrates containing an ethyl group reacted smoothly to provide the desired tetrahydrofuro[3,2-*d*]oxazoles (**2n–2t**, respectively) in good yields. The above results indicate the generality of the method in preparing tetrahydrofuro[3,2-*d*]oxazoles in this new and highly efficient way.

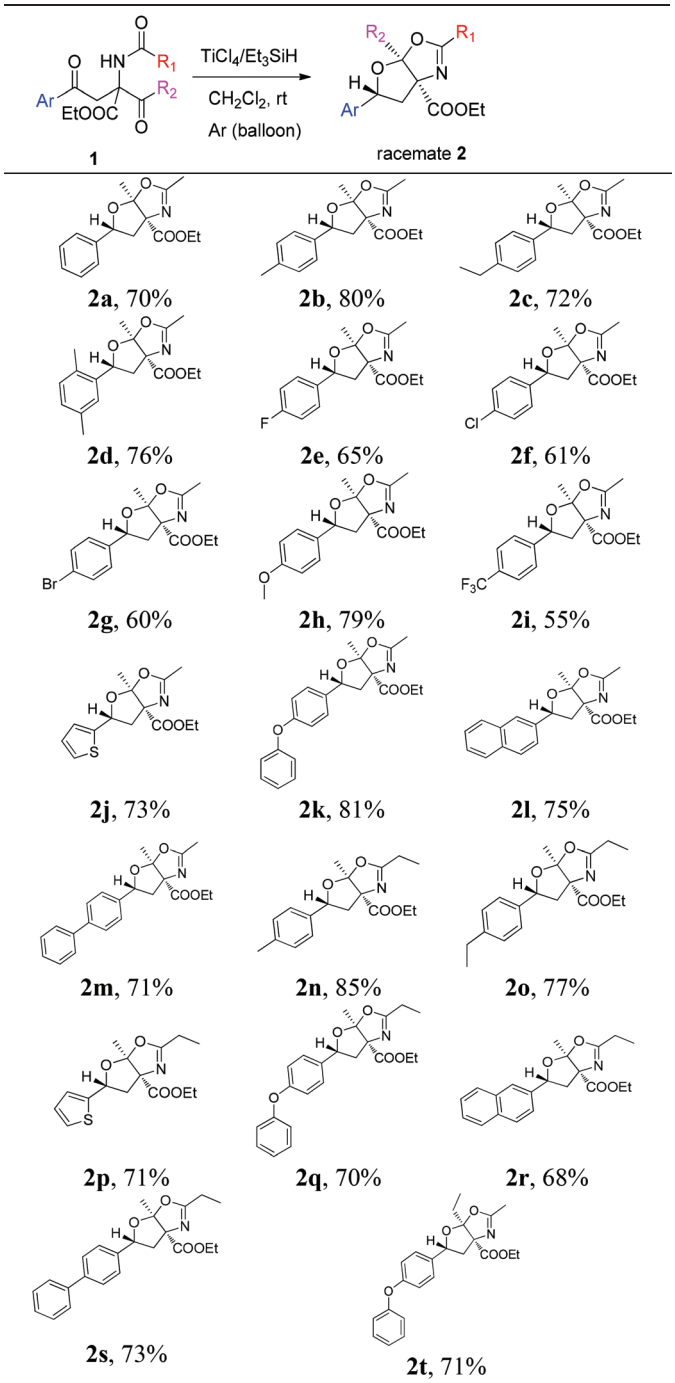
To further study the substrate-controlled stereoselectivity of this reaction, chiral separation of racemate **1k** on a Chiralcel AD-H column was employed to provide the chiral starting material (*S*)- and (*R*)-**1k**. The absolute configuration was confirmed by circular dichroism spectra. Both (*S*)-**1k** and (*R*)-**1k** could be smoothly converted to the corresponding chiral **2k**, respectively, with over 99% ee and dr > 99 : 1 (Scheme 4).

A plausible mechanism to rationalize this transformation is illustrated in Scheme 5. There are four carbonyls in the substrate (*S*)-**1a**. The real catalyst–reactant complex is not easy to be captured. The complexation of benzyl carbonyl and acetyl-



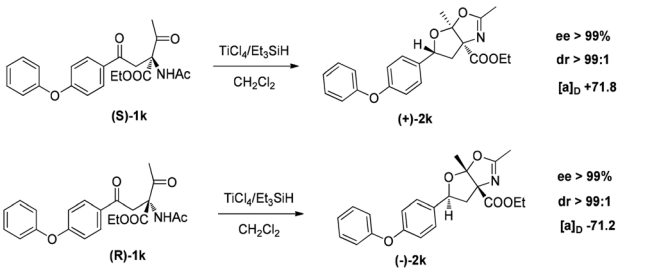
Scheme 3 Synthesis of arene-1,4-dione substrates **1**.

Table 2 Heterocyclization from arene-1,4-dione[a,b]

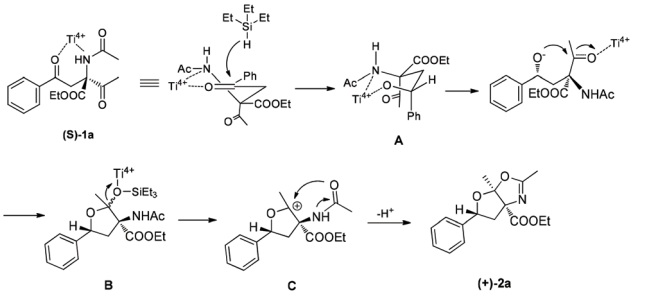


[a] Reaction conditions: arene-1,4-dione **1** (0.5 mmol), $TiCl_4$ (1.91 mmol), Et_3SiH (0.55 mmol), CH_2Cl_2 (5 mL) at room temperature under an argon atmosphere for 4 h. [b] Isolated yield.

amino with titanium was finally proposed to form a stable six-membered cyclic half-chair intermediate. Large group COOEt and Ac(NH) were more stable in equatorial orientation. The reductant Et_3SiH preferentially attacked on the less-encumbered side of the plane. According to this proposal, the benzyl



Scheme 4 Substrate-controlled stereoselective synthesis of chiral **2k**.



Scheme 5 Proposed mechanism for the formation of (+)-**2a**.

carbonyl of (*S*)-**1a** was firstly stereoselectively reduced to afford intermediate **A**, promoted by $TiCl_4$ using ionic hydrogenation. Then the ketalization intramolecularly led to the formation of intermediate **B**, whereas intermediate **B** could be easily converted to intermediate **C** by strong Lewis acid according to the literature.[7] Finally, the neighboring acetamido group led to a protonated oxazoline which could be deprotonated by the triethylsilanolate anion to afford the desired product (+)-**2a**.

Conclusions

In conclusion, an efficient and versatile method for the construction of a tetrahydrofuro[3,2-*d*]oxazole scaffold has been developed. Starting from easily accessible arene-1,4-diones, these heterocycles are stereoselectively formed in a cascade of ionic hydrogenation, ketalization, and intramolecular cyclization at room temperature. The efficiency and substrate scope of this reaction have been demonstrated by the formation of a wide range of functionalized tetrahydrofuro[3,2-*d*]oxazoles. Mild conditions, high efficiency, and simple procedure render this cascade reaction an attractive method in preparing tetrahydrofuro[3,2-*d*]oxazoles. Extension of the present reaction toward the synthesis of related heterocyclic moieties and detailed mechanistic investigations are currently in progress in our laboratory.

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