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COMMUNICATION

Domino alkylation/oxa-Michael of 1,3-cyclohexanediones: Steering the *C*/*O*-chemoselectivity to reach tetrahydrobenzofuranones†‡

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An unprecedented domino synthesis of tetrahydrobenzofuran-4-ones is described implicating chemoselective alkylation of various 1,3-cyclohexanediones with bromocrotonate or crotonitrile followed by oxa-Michael cyclization. Further transformations of this core to reach molecular diversity are also presented.

Substituted tetrahydrobenzofuran-4-one (TBF) structure and their derivatives are present in a variety of natural products, pharmaceuticals and diverse synthetic intermediates, the phyllaemblic acid methyl ester[1] and maoecrystal V[2] being examples of interest (Fig. 1). As an annelated structure of 2,3-dihydrofuran,[3] the TBF scaffold features a vinylogous ester and different entry points (R_1–R_4) which are valuable for reaching molecular diversity. The synthesis of the TBF core is a dynamic field of investigation and several recent ingenious strategies have been devised using 1,3-cyclohexanedione and electrophiles.[4] For example, the "interrupted" Feist–Bénary reaction enables the synthesis of TBFs by 1,2-addition of 1,3-cyclohexanedione to haloketones or epoxyaldehydes.[5] Alternatively, 1,3-cyclohexanedione was transformed to TBFs by reaction with alkenes activated by oxidizing reagents.[6] Starting from 1,3-diketones, domino reactions[7] have been developed with an emphasis on the 1,2- and 1,4-addition to electrophiles.[8] Given this background, we were interested in a domino process that could provide the TBF scaffold with different substitutions and distribution of regioisomers thanks to a new synthetic pathway. Hence, the alkylation of 1,3-cyclohexanedione with methyl 4-bromocrotonate followed by the oxa-Michael cyclization was expected to provide the TBF core with the desired substitutions (Scheme 1a). The regioselectivity of the oxa-Michael cyclization, which is so far unexplored, is interesting to examine with an unsymmetrical alkylated 1,3-cyclohexanedione such as **2** and **2′** prepared from **1** leading to cyclized products **3** and/or **3′**

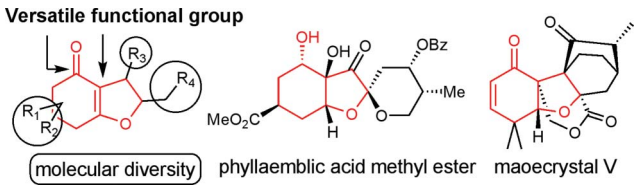

Fig. 1 The tetrahydrobenzofuran-4-one structure and selected examples of derivatives containing natural products.

(Scheme 1b). This strategy raises issues of reactivity and selectivity. Regarding the alkylation of the diketone, factors such as the low reactivity of the stabilized anion obtained in the presence of a base and the chemoselectivity of the reaction are difficult to tackle.[9–11] Moreover, the intramolecular oxa-Michael cyclization of acidic 1,3-cyclohexanedione ($pK_a \approx 10.5$ in DMSO) has scarcely been exploited due to the competing ring opening retro oxa-Michael process during which the C–O bond is broken.[12,13a]

We report herein a new domino process successfully implementing all the elements of this strategy in which the *C*-alkylation of 1,3-cyclohexanedione to 4-bromocrotonate (and derivatives) is followed by oxa-Michael cyclization to furnish TBF structures with fair to good yields. Furthermore, the oxa-Michael cyclization of **1** displayed promising and unprecedented regioselectivities.

We started by investigating the reaction of 1,3-cyclohexanedione with the commercially available methyl 4-bromocrotonate **A** (Scheme 2).

Under classical conditions (KOH, Cu cat., H_2O), 1,3-cyclohexanedione reacted poorly with methyl 4-bromocrotonate **A** providing the alkylated product **4** in 18% yield with 40% conversion and no chemoselectivity.[14] After a screening of bases and solvents, the combination of LiOH in 2,2,2-trifluoroethanol (TFE) and H_2O (Scheme 2, conditions a) gave encouraging yields of **4** (35%) and the cyclized adduct **5** (25%).

Enriching the media in TFE and heating at 45 °C (Scheme 2, conditions b) allowed the direct preparation of **5** in 64–72% yields with a chemoselectivity of 5 : 1. The use of TFE is crucial for both the chemoselective alkylation and the cyclization since the ring opening by the retro oxa-Michael process (**5**→**4**) occurred swiftly when **5** was treated by NaOH in MeOH. Given the acidity of TFE (pK_a 12.4 in H_2O),[13b] the hydroxylate (CF_3CH_2OLi) is generated by reaction of the excess of LiOH with the solvent. Subsequently, this weak base promotes the oxa-Michael cyclization without

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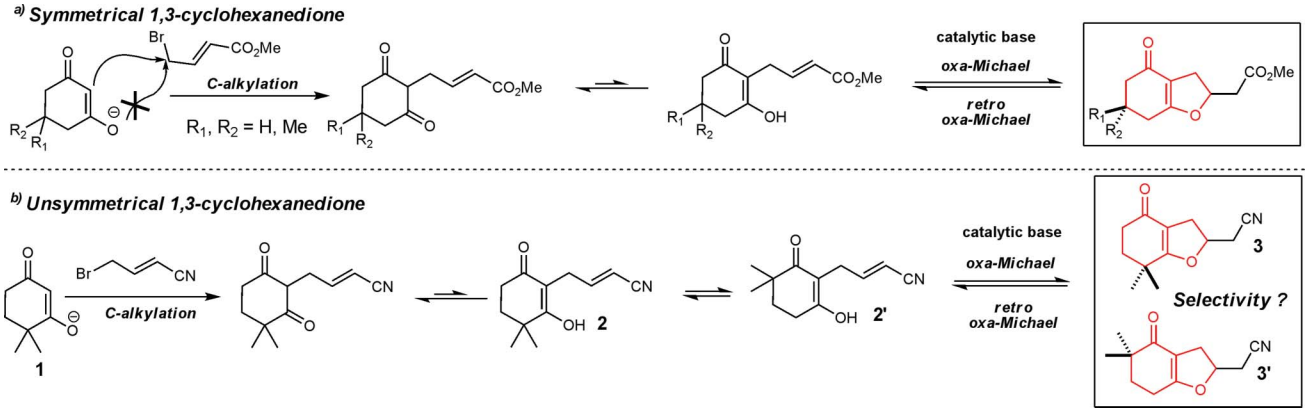
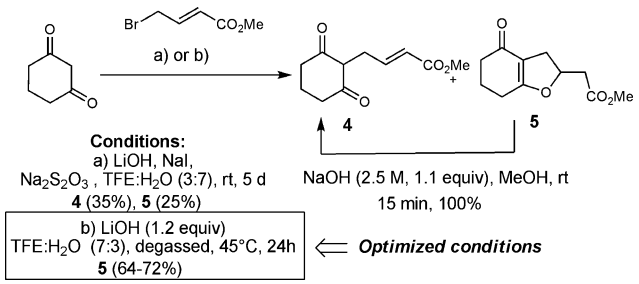
‡ Electronic supplementary information (ESI) available: Experimental procedures, ^1H and ^{13}C NMR spectra of new compounds, and crystallographic data for **6**. CCDC reference number 818360. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05923h



Scheme 1 Alkylation and oxa-Michael cyclization of symmetrical and unsymmetrical 1,3-cyclohexanediones.



Scheme 2 Optimization of the alkylation/cyclization sequence.

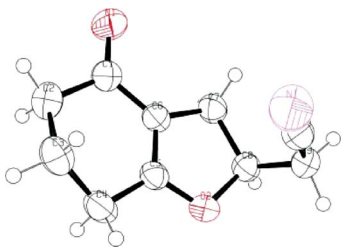


Fig. 2 ORTEP representation of **6** with thermal ellipsoid at 50% of probability.

triggering the reverse reaction whereas a stronger base would promote the retro oxa-Michael of **5**.

The domino process was successfully extended to 4-bromocrotonitrile **B** and 4-bromopent-2-enenitrile **C** producing the corresponding nitriles **6** and **7**. The results are summarized in Table 1. In the presence of **B**, prepared by radical bromination of crotonitrile, the alkylation/cyclization process of 1,3-cyclohexanedione yielded **6** in 58–75% yields with the *O*-alkylation side reaction greatly reduced (*C*/*O*, 10 : 1). Interestingly, the racemate of **6** has the peculiar characteristic of crystallizing as a conglomerate, a mixture of enantiomerically pure crystals of *R*-**6** and *S*-**6** (Fig. 2).

Prepared by radical bromination of commercially available 2-pentenenitrile, the electrophile **C** displayed lower reactivity but the yield of the process reached 45% despite strong *O*-alkylation competition (*C*/*O*, 2.5 : 1). Significantly, the *trans* isomer of **7** was predominant (10 : 1). Substituted symmetrical and unsymmetrical 1,3-cyclohexanediones, commercially available or prepared in one step,[15] were next evaluated for the domino process (Table 2).

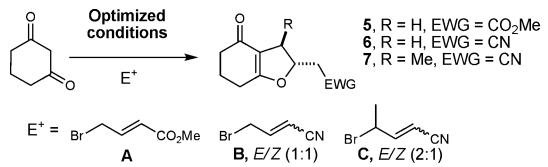
The 5,5-dimethyl-1,3-cyclohexanedione (dimedone) reacted with **C** yielding the bicycle **8** with a fair yield of 53% and good *trans* selectivity (Table 2, Entry 1).

Unsymmetrical 4,4-dimethyl-1,3-cyclohexanedione **1** proved to be an interesting nucleophile to evaluate for this domino process. Indeed, the reaction of **1** with methyl 4-bromocrotonate **A** led to the formation of the major isomer **9** and minor isomer **9′** in a ratio of 2 : 1 and 58% yield (Table 2, Entry 2).[16] When 4-bromocrotonitrile **B** was employed, **3** and **3′** were obtained with higher regioselectivity of 3 : 1 and yields of 61–68% (Table 2, Entry 3). The hindered bromide **C** displayed selectivity of 2 : 1 (**10** : **10′**) when reacted with **1** (46% yield, Table 2, Entry 4). The substitution of the diketone had an impact on the regioselectivity of the cyclization since the monosubstituted diketone **11** (Table 2, Entry 5) displayed no selectivity when reacted with **C**.

Having established a protocol for the rapid preparation of the TBF structures, we sought to exploit the reactivity of each functional group present in these molecules to generate further molecular diversity (Scheme 3). These substrates exhibit both an ester (or nitrile) and a vinylogous ester and addressing their specific reactivity may be challenging.

Hence, eqn (1), Scheme 3, describes the stereoselective reduction of the vinylogous ester of **5** (H_2, Pd/C, TFA, EtOH) to produce annelated 2,3,5-*cis*-trisubstituted tetrahydrofuran **13** (68%). The use of trifluoroacetic acid (2 equiv) was crucial to the success of this transformation since a complex mixture was obtained without it. Subsequently, **13** was submitted to Baeyer–Villiger oxidation (eqn (2)) promoted by trifluoroperacetic acid to deliver

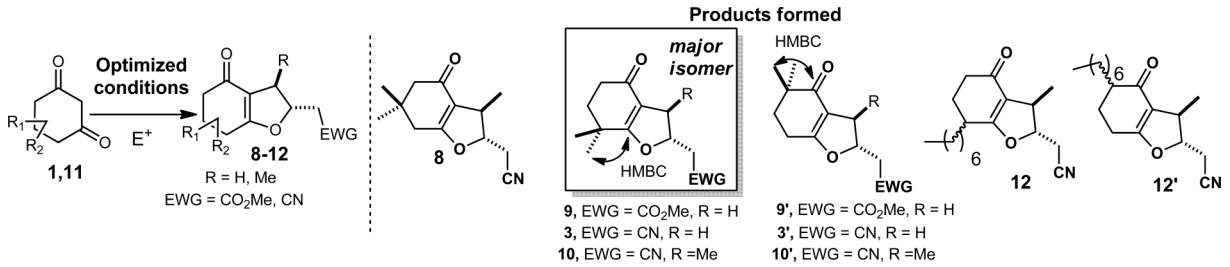
Table 1 Domino transformation of 1,3-cyclohexanedione



Entry	Electrophile	Ratio *C*/*O*	Time (day)	Products (yields)
1	**A**	5 : 1	2	**5** (64–72%)
2	**B**	10 : 1	1	**6** (58–75%)
3	**C**	2.5 : 1	5	**7** (45%)[a]

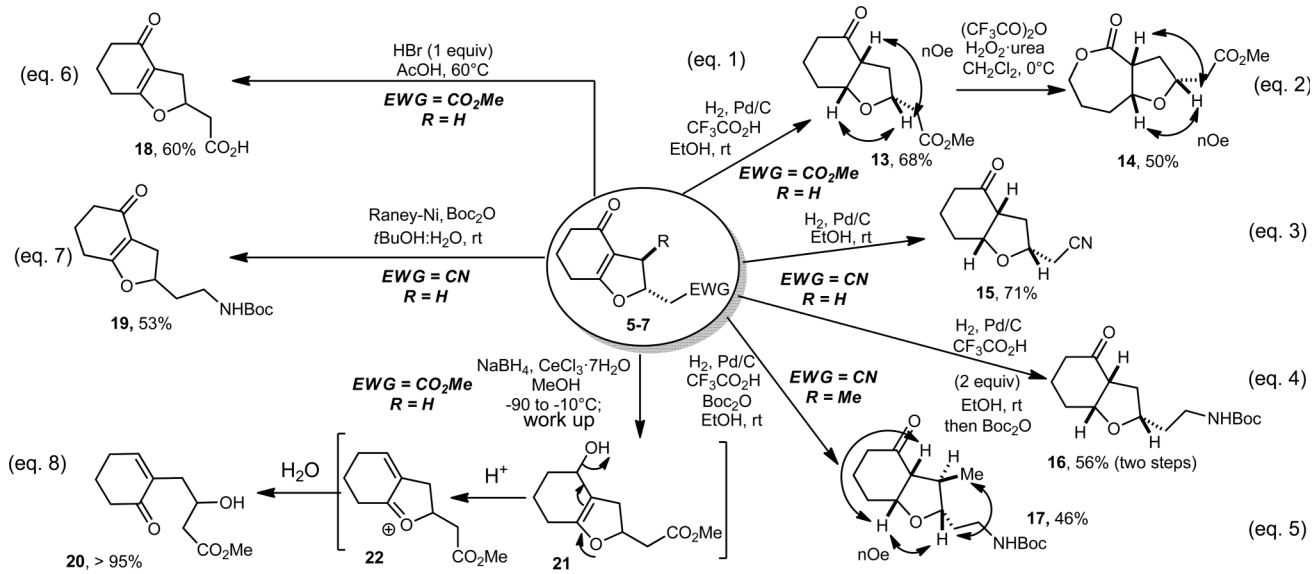
[a] Reactions performed at 60 °C, *trans*/*cis* selectivity of 10 : 1.

Table 2 Domino transformation of symmetrical and unsymmetrical 1,3-cyclohexanediones



Entry	Nucleophiles	Electrophiles	Ratio of regioisomers[a]	*Trans*/*Cis*[a]	Products (yields)[b]
1	Dimedone, $R_1 = R_2 = 5,5\text{-Me}$	**C**	—	10 : 1	**8** (53%)
2	**1**, $R_1 = R_2 = 4,4\text{-Me}$	**A**	2 : 1, (**9** : **9′**)	—	**9**/**9′** (58%)
3	**1**, $R_1 = R_2 = 4,4\text{-Me}$	**B**	3 : 1, (**3** : **3′**)	—	**3**/**3′** (61–68%)
4	**1**, $R_1 = R_2 = 4,4\text{-Me}$	**C**	2 : 1, (**10** : **10′**)	10 : 1	**10**/**10′** (46%)
5	**11**, $R_1 = 4\text{-H}$, $R_2 = 4\text{-}n\text{C}_7\text{H}_{16}$	**C**	1 : 1, (**12** : **12′**)	10 : 1	**12**/**12′** (39%)

[a] Determined by ^{1}H NMR, HMBC and NOESY analyses. [b] Isolated yields.



Scheme 3 Molecular diversity from the tetrahydrobenzofuran-4-one structures.

the "abnormal" isomer of the 7-membered ring lactone **14** in 50% yield.[17] The vinylogous ester of **6** was selectively reduced into **15** without affecting the nitrile group (H_2, Pd/C, EtOH, 71%, eqn (3)). The stereoselective reduction of both the vinylogous ester and the nitrile of **6** and **7** was performed (H_2, Pd/C, TFA, EtOH; Boc_2O) yielding the *cis*-trisubstituted tetrahydrofuran **16** (56%, eqn (4)) and the tetrasubstituted tetrahydrofuran **17** (46%, eqn (5)). It is interesting to note that the methyl substituent of the 2,3-dihydrofuran ring did not influence the stereoselectivity of the hydrogenation of **7** since **16** and **17** share the same relative configuration. The saponification of the methyl ester group of **5** was complicated by the retro oxa-Michael reaction occurring in presence of bases. However, after treatment of **5** with HBr (eqn (6)), carboxylic acid **18** was isolated in 60% yield. The nitrile group of **6** was chemoselectively reduced in presence of Raney-Ni (eqn (7)) to deliver amine **19** in 53% yield. In the case of **5**, the carbonyl of the vinylogous ester was reduced under Luche conditions (eqn (8)) to deliver directly and in quantitative yield α-substituted cyclohexenone **20**. The formation of **20** may take place by hydrolysis of allylic alcohol **21** into oxonium **22** after 1,2-reduction of the carbonyl of **5**.

A new and simple access to substituted tetrahydrobenzofuran-4-one molecules has been opened up. The chemoselective alkylation of 1,3-cyclohexanediones to substituted 4-bromocrotonate/crotonitrile is the initial step of this domino process. In these conditions, the alkylated 1,3-cyclohexanedione next undergoes a diastereoselective oxa-Michael cyclization (up to 10 : 1), while the retro oxa-Michael process is prevented. Furthermore, the cyclization displayed promising and unprecedented regioselectivities (up to 3 : 1) when performed with unsymmetrical 4,4-dimethyl-1,3-cyclohexanedione. Versatile and stereoselective 1–3 step chemical transformations were also demonstrated on these substrates to reach molecular diversity from readily available reagents and using undistilled solvents.

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