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An expedient stereoselective and chemoselective synthesis of bicyclic oxazolidinones from quinols and isocyanates†

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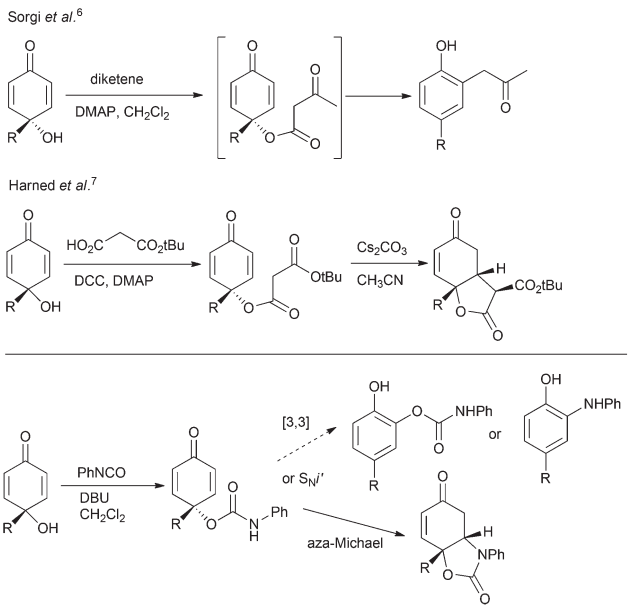
A mild and efficient synthesis of bicyclic oxazolidinones from quinols and isocyanates, under DBU-mediated conditions at room temperature, is described. The aza-Michael addition to substituted cyclohexadienones is stereoselective and chemoselective.

Quinols are important skeletons frequently found in bioactive natural products.[1] They are also useful synthetic building blocks, serving as valuable intermediates in the total synthesis of natural products.[2] One of the main reaction sites on quinols is the tertiary alcohol moiety. A well-known reaction involving this site is cyclohexadienone–phenol rearrangement,[3] which leads to either hydroquinone or resorcinol products.[4] Recently new attention has been focused on asymmetric desymmetrization of the double bonds in quinol derivatives.[5] Sorgi *et al.* found that reaction between quinol and diketene in the presence of a catalytic DMAP afforded a [3,3]-sigmatropic rearrangement product arylacetone.[6] On the other hand, Harned and coworkers recently prepared bicyclic lactones *via* an intramolecular Michael addition of quinol malonates.[7] The subtle difference between the starting materials (acetoacetates *vs*. malonates) led to markedly different products, demonstrating rich reactivity in the cyclohexadienone setting in quinol derivatives.

Thermal or acid-mediated migration of the acyloxy group around the cyclohexadienone ring in quinol esters through a [3,3]- or [1,3]-sigmatropic rearrangement has been known.[8] Moreover, mercury-promoted and anionic [3,3]-sigmatropic rearrangements for carbamates have also been reported.[9] Although carbamates have been reported to undergo intramolecular Michael addition to unsaturated esters,[10] the big driving force of aromatization after a [3,3]-sigmatropic rearrangement or an S_Ni' reaction in the quinol system could affect the reactivity. Therefore, we decided to explore the reaction between quinols and isocyanates to see whether a [3,3]-sigmatropic rearrangement or an aza-Michael addition ensues after formation of the carbamate intermediates (Scheme 1). A [3,3]-sigmatropic rearrangement or an S_Ni' reaction would lead to phenols as products, while the aza-Michael reaction would afford bicyclic oxazolidinones. Oxazolidinones are an important family of compounds widely used as chiral auxiliaries,[11] ligands for metal catalysis,[12] and antibiotics against methicillin-resistant, vancomycin-resistant and penicillin-resistant pathogens.[13] Synthesis of oxazolidinones has been well-documented in the literature.[14] Many new methods have been developed recently, such as IBX-mediated cyclization of carbamates,[15] Hofmann rearrangement of hydroxypropionamide,[16] iron(II)-catalyzed nitrogen transfer of unsaturated



Scheme 1 Synthetic plan.

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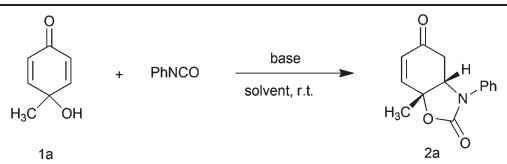
alkoxycarbonyl azides,[17] rhodium-[18] and silver-catalyzed[19] C–H insertion of carbamates, and iron(II)-catalyzed aminobromination of allyl *N*-tosyloxy-carbamates.[20] We reported herein our findings on the one-step stereoselective and chemoselective synthesis of bicyclic oxazolidinones from quinols.

Under Sorgi's conditions[6] quinol **1a** reacted with phenyl isocyanate afforded 30% yield of a product which was characterized as 3a,7a-dihydro-7a-methyl-3-phenyl-2,5(3*H*,4*H*)-benzoxazoledione (a bicyclic oxazolidinone) **2a**, an aza-Michael product from the carbamate intermediate. Under Harned's conditions[7] (Cs_2CO_3, CH_3CN), a messy mixture of products was obtained. We next optimized the conditions for cyclization and found that the reaction gave the best yield when DBU was chosen as the base and methylene chloride as the solvent (see Table 1).

Using a wide range of quinols, which are readily prepared in one step from commercially available phenols,[21] we explore the generality of this reaction with phenyl isocyanate. Representative results are shown in Table 2. For unsubstituted quinols, stereoselective addition gave *cis*-fused bicyclic oxazolidinones in good to excellent yields (**2a–2i**). The relative configuration of *cis* ring fusion was confirmed by NOESY spectroscopy data and further confirmed by X-ray crystallography‡ (compounds **2n**, **2q** and **2x**). For monosubstituted quinols, the substrates cyclized chemoselectively to the unsubstituted conjugate double bonds (**2j–2n**). For bromo quinol **1m**, surprisingly, our result was different from the cyclization of quinol malonates reported by the Harned group.[7] Harned and coworkers obtained a cyclopropane product **4** which resulted from cyclization from the more electron-deficient bromo-substituted double bond in malonate **3** (Scheme 2). While in our case, the nitrogen added to the unsubstituted double bond, which was clearly indicated by one nonaromatic alkenic proton and two methylene protons in the proton NMR

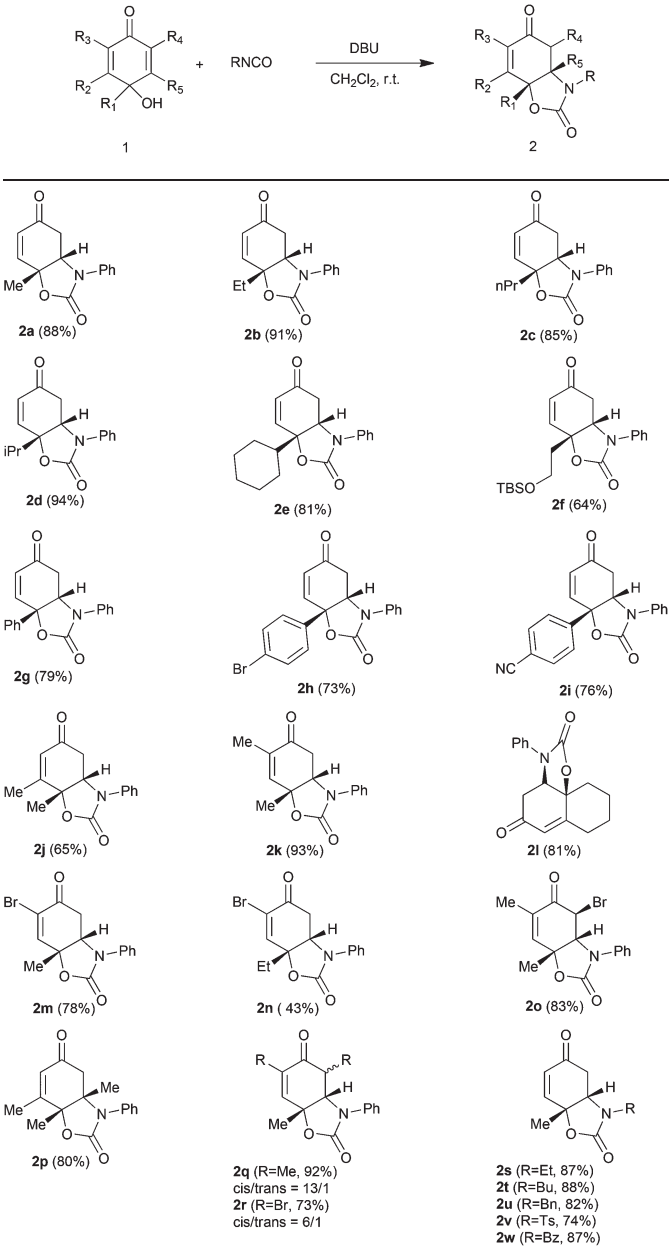
Table 1 Optimization of the reaction conditions[a]

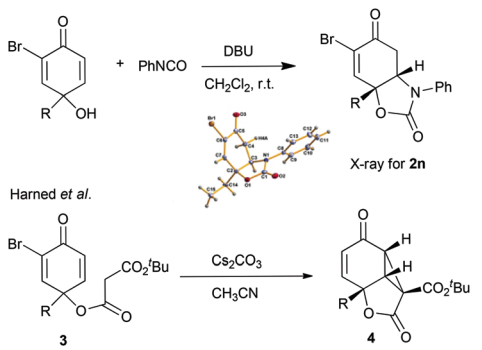


Entry	Base	Solvent	Yield[c] (%)
1	DMAP[b]	CH_2Cl_2	31
2	Cs_2CO_3	CH_3CN	Messy
3	Cs_2CO_3	CH_2Cl_2	Messy
4	NaH	THF	Messy
5	DBU[b]	CH_3CN	62
6	DBU	CH_2Cl_2	**88**
7	DBU	THF	69
8	DBU	$CHCl_3$	70
9	DBU	Toluene	56

[a] Unless otherwise noted, all reactions were performed with **1a** (0.3 mmol), PhNCO (0.36 mmol), base (15 mol%) in solvent (2 mL) at room temperature for 3 h. [b] DMAP: 4 dimethylamino-pyridine; DBU: 1,8-diazabicycloundec-7-ene. [c] Isolated yields.

Table 2 Substrate scope of the stereoselective cyclization





Scheme 2 Different modes of cyclization.

of **2m**. Furthermore, the structure of **2n** was unambiguously confirmed by X-ray crystallography. For reaction of bromo quinols with alkyl isocyanates, only an intractable messy mixture was obtained. Neither oxazolidinones nor aziridines could be isolated. The mode of cyclization of bromo quinols is governed by a subtle stereoelectronic effect, as further demonstrated in substrate **2o**. Since a bromo substituent is similar in size to a methyl group, the inductive effect of the bromo group controlled the cyclization mode in **2o**. The stereochemistry of **2o** was determined by comparison of its coupling constant with that of **2q**. For 3,5-disubstituted quinol **1p**, cyclization afforded **2p** in good yield. For 2,6-disubstituted quinols **1q** and **1r**, an inseparable mixture of isomers was obtained. All-*cis* isomers are the major products according to nOe spectroscopy. For **2q**, two recrystallizations afforded the pure *cis* isomer, whose stereochemistry was confirmed by X-ray crystallography (Fig. 1). It should be noted that the stereochemistry of the alpha methyl to the carbonyl group in **2q** is different from the Harned's lactone cases.[7] To further explore the scope of this reaction, we next focused on the generality of the addition partner isocyanates. Ethyl isocyanate, butyl isocyanate, benzyl isocyanate, benzoyl isocyanate and tosyl isocyanate are all good partners to afford good to excellent yields (**2s–2w**). Bicyclic 4-hydroxycyclohexenone **1x**[21a] is also a good substrate for the aza-Michael addition, which afforded tricyclic oxazolidinone **2x** as the product (Scheme 3).

In conclusion, we have developed a one-step stereoselective and chemoselective synthesis of bicyclic oxazolidinones from quinols in good to excellent yields. Starting from readily available phenols and isocyanates it affords oxazolidinones in an effective two-step procedure. These highly functionalized heterocycles could be of interest to the pharmaceutical industry. Synthesis of aminocyclitols and carbazoles from these oxazolidinones is ongoing in our lab.

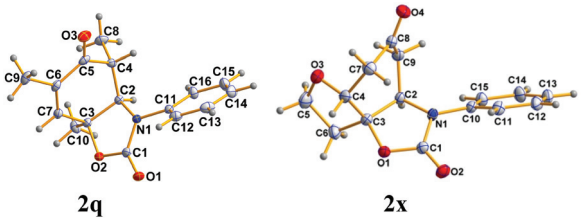
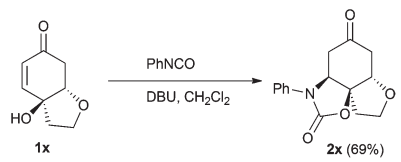


Fig. 1 Molecular structures of **2q** and **2x** with ellipsoids set at 50% probability level.



Scheme 3 Synthesis of tricyclic oxazolidinone.

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Notes and references

‡Crystal data: **2n**: $C_{15}H_{14}BrNO_3$, M = 336.18, monoclinic, space group $P2_1/c$, a = 11.3435(10), b = 5.9481(5), c = 20.6935(18) Å, β = 103.5110(10)°, V = 1357.6(2) Å^3, T = 100(2) K, Z = 4, 25 544 reflections measured, 3362 independent reflections (R_{int} = 0.0479); R_1 = 0.0248 ($I > 2\sigma(I)$), 0.0338 (all data); w$R(F^2)$ = 0.0532 ($I > 2\sigma(I)$), 0.0564 (all data); CCDC number 916845. **2q**: $C_{16}H_{17}NO_3$, M = 271.31, monoclinic, space group $P2_1/c$, a = 14.8275(13), b = 7.8956(7), c = 11.8515(11) Å, β = 94.9930(10)°, V = 1382.2(2) Å^3, T = 100(2) K, Z = 4, 26 236 reflections measured, 3432 independent reflections (R_{int} = 0.0326); R_1 = 0.0354 ($I > 2\sigma(I)$), 0.0409 (all data); w$R(F^2)$ = 0.0897 ($I > 2\sigma(I)$), 0.0945 (all data); CCDC number 921685. **2x**: $C_{15}H_{15}NO_4$, M = 273.28, monoclinic, space group $P2_1/n$, a = 6.1123(4), b = 17.9740(12), c = 11.7487(8) Å, β = 96.0380(10)°, V = 1283.58(15) Å^3, T = 100(2) K, Z = 4, 26 919 reflections measured, 3196 independent reflections (R_{int} = 0.0302); R_1 = 0.0424 ($I > 2\sigma(I)$), 0.0483 (all data); w$R(F^2)$ = 0.1124 ($I > 2\sigma(I)$), 0.1176 (all data); CCDC number 916844.

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