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N-Heterocyclic Carbene Catalyzed Annulation of Enals to Aurone Analogs: Synthesis of Cyclopentene-Fused Spirobenzofuran-3-ones

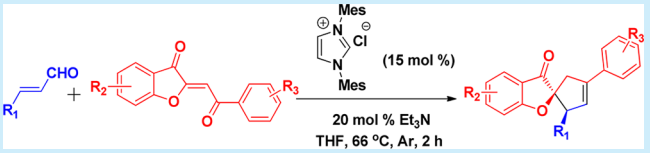
K. C. Seetha Lakshmi,[†,‡] Jagadeesh Krishnan,[†] C. R. Sinu,[†] Sunil Varughese,[†] and Vijay Nair*[,†]

[†]Chemical Science and Technology Division, National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Trivandrum-695 019, India

[‡]School of Chemical Sciences, Mahatma Gandhi University, Kottayam-686 560, India

Supporting Information

ABSTRACT: A nucleophilic heterocyclic carbene mediated homoenolate annulation of enals to aurone analogs leading to the efficient synthesis of cyclopentene-fused spirobenzofuran-3-ones is reported.

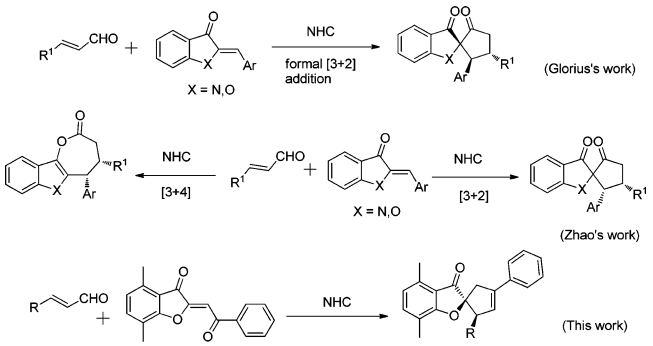


The renaissance of organocatalysis[1] in recent years has rekindled interest in the design and execution of synthetic protocols catalyzed by N-heterocyclic carbenes (NHC).[2] Consequently a number of powerful methods for the construction of C−C and C−heteroatom bonds have emerged after the independent demonstration by Glorius and Bode that homoenolates generated from enals by NHCs underwent annulation to aldehydes to afford γ-butyrolactones.[3,4] Subsequent investigations in different laboratories have revealed that homoenolates react with a wide range of electrophiles to afford cyclopentenes[5,6] and other cyclopentanoids,[7] lactams,[8] pyrazolidinones,[9] pyranones,[10] GABA analogs/precursors,[11] and assorted compounds.[12] Homoenolate reactions assisted by cooperative Lewis acid/NHC catalysis[13] and intramolecular processes[14] are also noteworthy. Catalytic transesterifications[15] by NHCs as well as work utilizing unsaturated acyl azolium species are also worthy of mention.[16]

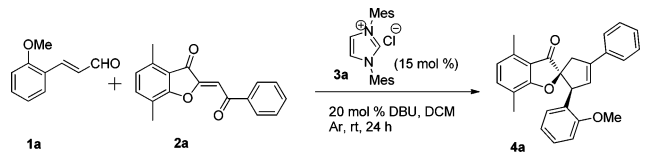
Ever since our first report[17a] on the synthesis of spirolactones by the homoenolate annulation of cyclic 1,2-diones and isatins, several groups, including our own, have contributed significantly to this area.[13c,17] Very recently it was observed that homoenolate underwent facile annulation to benzofuran-2,3-diones to afford bis-spirofuranones.[17e] The success of this reaction prompted us to examine the possibility of NHC-catalyzed enal annulation to aurone analogs with the assumption that such a process would yield cyclopentene-fused spiro-benzofuran-3-ones. Impetus for our endeavor was also derived from the fact that a number of benzofuran and aurone derivatives are known to exhibit potent pharmacological effects.[18] Quite coincidentally, while this manuscript was in preparation, Glorius and co-workers reported that aurones undergo homoenolate annulation to afford spiro-heterocycles.[19] Contemporaneously, Zhao and co-workers reported a stereoselective synthesis of benzofuran/indole-containing ε-lactones or spiro-heterocycles by the NHC-catalyzed annulation of enals with heterocyclic enones (Scheme 1).[20]

In a prototype experiment, 2-methoxycinnamaldehyde **1a**, 2-benzoylidene benzofuran-3-one **2a**, and IMesCl **3a** (15 mol %) were taken up in DCM. After the addition of DBU (20 mol %) the solution was allowed to stir at room temperature for about 24 h. The reaction mixture upon column chromatography afforded the product, cyclopentene-fused spiro-benzofuran-3-one **4a**, in 32% yield (Scheme 2).

Scheme 1. NHC-Catalyzed Annulation Reaction



Scheme 2. Homoenolate Reaction of Enal with 2-Benzoylidene Benzofuran-3-one



The alkenyl proton of the cyclopentenyl core was observed at δ 6.29 in the ^{1}H NMR spectrum. The ^{13}C resonance signal at δ 203.9 indicated the carbonyl carbon, supporting the IR absorption at 1709 cm^{-1}. The spiro carbon was discernible from the signal at δ 94.8. All the other signals were in good agreement with the assigned structure. Conclusive evidence for

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the structure and relative stereochemistry of **4a** was ascertained from the single crystal X-ray data (Figure 1).

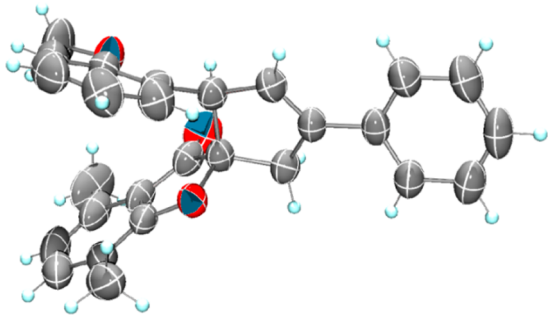
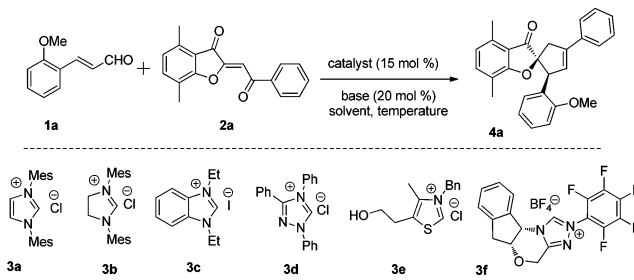


Figure 1. ORTEP diagram of **4a**.

In view of the pleasing result, optimization studies in detail were determined to be next. For this, commonly available NHC precursors **3a**–**f** were used for screening (Table 1). Among the

Table 1. Condition Optimization[a]



entry	catalyst	base	solvent, temperature (°C)	time (h)	yield[b] (%)
1	**3a**	DBU	DCM, rt	24	32
2	**3b**	DBU	DCM, rt	24	20
3	**3c**	DBU	DCM, rt	24	–
4	**3d**	DBU	DCM, rt	24	17
5	**3e**	DBU	DCM, rt	24	10
6	**3f**	Et_3N	THF, 66 °C	24	–
7	**3a**	Et_3N	DCM, rt	12	47
8	**3a**	K_2CO_3	DCM, rt	24	–
9	**3a**	DMAP	DCM, rt	24	–
10	**3a**	^{t}BuOK	DCM, rt	24	25
11	**3a**	Et_3N	DCM, 40 °C	3	50
12	**3a**	Et_3N	THF, rt	12	56
13	**3a**	Et_3N	toluene, rt	24	28
14	**3a**	Et_3N	CH_3CN, rt	24	–
15	**3a**	Et_3N	THF, 66 °C	2	76

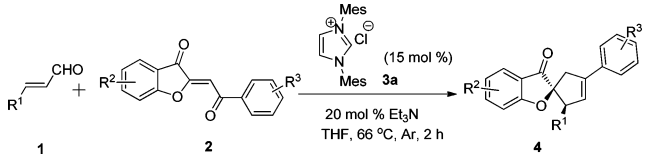
[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), carbene precursor (15 mol %), base (20 mol %) in 3 mL of solvent. [b]Isolated yield.

six catalysts investigated, imidazolium catalyst **3a** exhibited high catalytic activity (Table 1, entry 1). In contrast to the NHC precursor **3a**, imidazolinium catalyst **3b** gave the product in 20% yield (Table 1, entry 2) whereas the benzimidazolium salt **3c** failed to give the desired annulation product (Table 1, entry 3). While in the case of NHC precatalysts **3d** and **3e**, the product was isolated in lower yield (Table 1, entries 4 and 5).

After identifying NHC precursor **3a** as the optimal catalyst, we investigated the influence of base, solvent, and temperature on the reaction (Table 1). Among the four bases tested, Et_3N furnished the desired product in good yield (Table 1, entry 7). In comparison to Et_3N, ^{t}BuOK also afforded the annulation product, but the yield of the product was only 25% (Table 1, entry 10). Later we examined several solvents such as DCM, THF, toluene, and CH_3CN. Among them THF was found to be the best solvent under room temperature conditions (Table 1, entry 12). When toluene was used as the solvent, the product was formed in lower yield, but in the case of CH_3CN no reaction was observed (Table 1, entries 13 and 14). Finally, when the reaction was carried out in THF at 66 °C the product was formed in optimal yield (Table 1, entry 15). Based on the above results, it was clear that the formation of cyclopentene fused spirobenzofuran-3-one in higher yield was facilitated by the combination of imidazolium carbene precursor **3a** and Et_3N in THF as the solvent under reflux conditions.

Subsequent studies were focused on the scope of the reaction. As shown in Table 2, the reaction works well for a

Table 2. Scope of the Reaction[a]



entry	R^1	R^2	R^3	product	yield[b] (%)
1	2-$MeOC_6H_4$	4,7-Me_2	H	**4a**	76
2	4-$MeOC_6H_4$	4,7-Me_2	H	**4b**	63
3	Ph	4,7-Me_2	H	**4c**	68
4	furyl	4,7-Me_2	Cl	**4d**	61
5	4-ClC_6H_4	4,6-Me_2	H	**4e**	88
6	4-$NO_2C_6H_4$	4,6-Me_2	H	**4f**	46
7	4-BrC_6H_4	4,6-Me_2	Cl	**4g**	83
8	4-$MeOC_6H_4$	4-*i*-Pr-6-Me	H	**4h**	57
9	4-ClC_6H_4	4-*i*-Pr-6-Me	H	**4i**	63
10	4-$MeOC_6H_4$	4-Me-6-*i*-Pr	H	**4j**	71
11	4-ClC_6H_4	4-Me-6-*i*-Pr	H	**4k**	68
12	4-FC_6H_4	4,6,7-Me_3	H	**4l**	91
13	4-MeC_6H_4	4,6,7-Me_3	H	**4m**	74
14	4-ClC_6H_4	4,6,7-Me_3	Cl	**4n**	91
15	4-MeC_6H_4	4,6,7-Me_3	Cl	**4o**	70

[a]Reactions were carried out with **1** (0.15 mmol), **2** (0.1 mmol), carbene precursor (15 mol %), Et_3N (20 mol %) in 3 mL of dry THF (refluxed for 2 h). [b]Isolated yield.

range of enals having electron-withdrawing and -donating substituents. The reaction proceeds smoothly for different substituted 2-benzoylidene benzofuran-3-ones. In all the cases annulation products were obtained in moderate to good yields. Of note, the reaction of enal carrying a heteroaryl group proceeds effectively to give the product in 61% yield (Table 2, entry 4).

The scope of the reaction was further explored by employing *β*-alkyl substituted enals in the reaction. It was found that the method was successful in the synthesis of alkyl substituted cyclopentene fused spirobenzofuran-3-ones in good yields (Figure 2).

In view of the above results, it was of interest to study the reaction of dienal **1l** with 2-benzoylidene benzofuran-3-one **2e** under the optimal reaction conditions. Delightfully, 4,6,7-trimethyl-4′- phenyl-2′-((*E*)-prop-1-en-1-yl)-3*H*-spiro[benzo-

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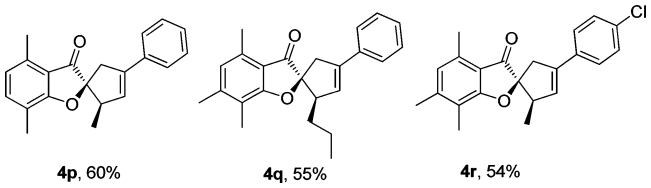
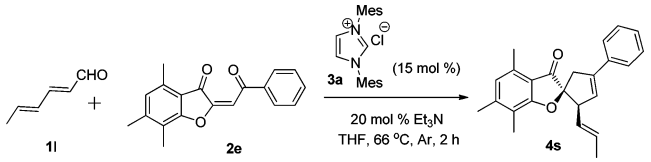


Figure 2. Annulation products obtained from aliphatic enals.

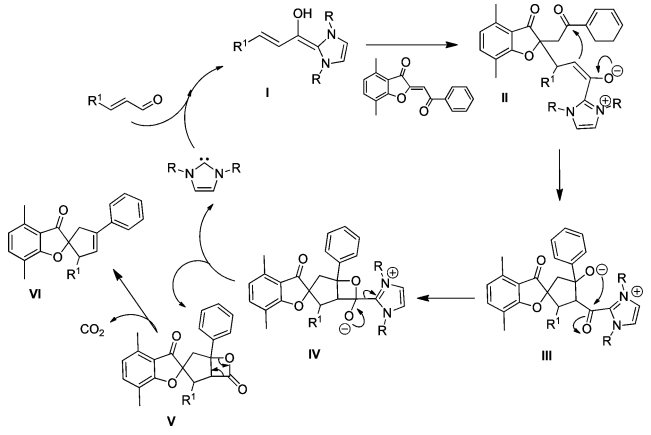
furan-2,1′-cyclopent[3]en]-3-one **4s**, endowed with an alkenyl chain, was obtained in 70% yield (Scheme 3).

Scheme 3. Reaction of Dienal with 2-Benzoylidene Benzofuran-3-one



A mechanistic rationalization for the formation of spirocyclopentene is as follows. The homoenolate **I** formed initially by the reaction of IMes with enal undergoes conjugate addition to 2-benzoylidene benzofuran-3-one and consequent to a proton transfer generates the enolate **II** which then participates in an intramolecular aldol reaction to afford the cyclopentane carbinolate **III**. The latter undergoes lactone formation accompanied by the ejection of IMes. The β-lactone **V** undergoes a retro-[2 + 2] process to yield the cyclopentene fused spiro-benzofuran-3-one **VI** with the loss of carbon dioxide (Scheme 4). It may be mentioned that the sequence of events

Scheme 4. Mechanistic Rationale



presented here is analogous to the one that was established experimentally[5a] and theoretically[21] for the 1,3,4-triaryl cyclopentene synthesis reported earlier.

In conclusion we have developed a novel NHC-catalyzed homoenolate annulation to 2-aroylidene benzofuran-3-ones leading to the synthesis of cyclopentene-fused spirobenzofuran-3-ones. It is noteworthy that a wide range of natural products and biologically active derivatives contain a 2-spirocyclic benzofuran-3-one framework.[22] It is conceivable that the protocol outlined herein may be applicable to the synthesis of biologically relevant molecules.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vijaynair_2001@yahoo.com.

Notes

The authors declare no competing financial interest.

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