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N-Heterocyclic Carbene Catalyzed Reaction of Enals and 1,2-Dicarbonyl Compounds: Stereoselective Synthesis of Spiro γ-Butyrolactones

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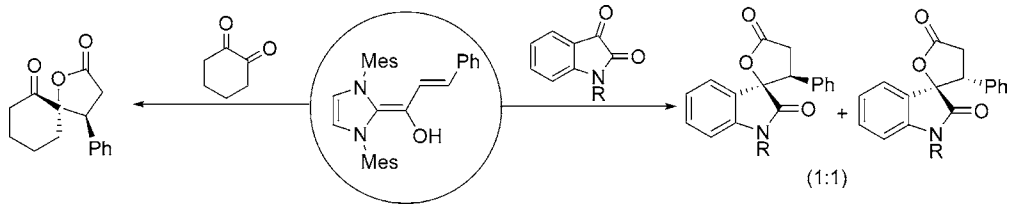
ABSTRACT



Nucleophilic heterocyclic carbene (NHC) catalyzed annulation of enals and cyclic 1,2-dicarbonyl compounds, opening a route to γ-spirolactones, has been observed for the first time. The strategy works well with isatins, leading to spiroannulated oxindole derivatives. It is conceivable that the spiroannulation protocol reported herein will be applicable to the synthesis of important natural products that are endowed with a spiro γ-butyrolactone motif, especially oxindoles and norsesquiterpenoids.

In his original work in 1958, Breslow[1] conceptualized and demonstrated that nucleophilic heterocyclic carbenes (NHCs) derived from a number of azolium species, viz., thiazolium, imidazolium, and benzimidazolium salts, catalyze the benzoin condensation. Subsequently, NHCs have been utilized effectively in a number of transformations such as the Stetter reaction,[2] formoin condensation,[3] etc. In recent years, consequent to the awareness of their excellent ligating properties[4] and isolation of stable NHCs by Arduengo,[5] there has been renewed interest in these unique and powerful reactive intermediates,[6] especially from the vantage point of organocatalysis[7] and their participation in multicomponent reactions.[8] The use of NHCs in transesterification[9] and acylation reactions,[10] asymmetric catalysis of the Stetter reaction,[2] and the synthesis of dihydroxyacetone as well as

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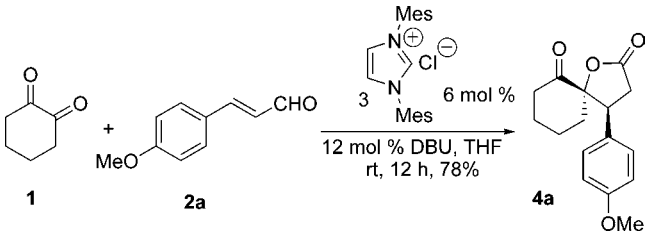
carbohydrates is particularly noteworthy.[3a,11] Very recently, an NHC catalyzed annulation of enals and aldehydes leading to an efficient synthesis of γ-butyrolactones was reported independently by Bode[12] and Glorius.[13] The reaction proceeds via the transformation of an enal to a homoenolate.[14,15] Subsequent work by Bode has shown that this annulation is applicable to the synthesis of γ-lactams[16] albeit to a limited extent. Ketones, with the exception of α,α,α-trifluoroacetophenone, failed to undergo annulation.[13] In the context of our interest in the chemistry of 1,2-diones[17] and in the perception that the homoenolate annulation, although generally unsuccessful with ketones, was likely to succeed with 1,2-diones, we undertook some investigations in this area. A considerable incentive for such studies was derived from the prospect of a successful reaction opening a route to γ-spirolactones. The results of our work are presented in this letter.

Our studies were initiated by exposing a mixture of 4-methoxycinnamaldehyde and 1,2-cyclohexane dione to a catalytic amount (6 mol %) of 1,3-dimesityl imidazol-2-ylidene (IMes) **3**. A slow but efficient reaction occurred, and the spiro γ-butyrolactone **4a** was obtained as a single diastereomer (Scheme 1).

Scheme 1. Reaction of 4-Methoxycinnamaldehyde with 1,2-Cyclohexanedione



The structure of the product **4a** was assigned by spectroscopic analysis. The benzylic proton resonated as a triplet centered at δ 3.66 in the ^{1}H NMR spectrum. The lactone and keto carbonyl groups displayed ^{13}C resonance signals at δ 174.2 and δ 205.8, respectively, supporting the IR absorptions at 1775 and 1723 cm^{-1}. The final confirmation of the structure and stereochemistry of **4a** was obtained from single-crystal X-ray analysis (Figure 1).

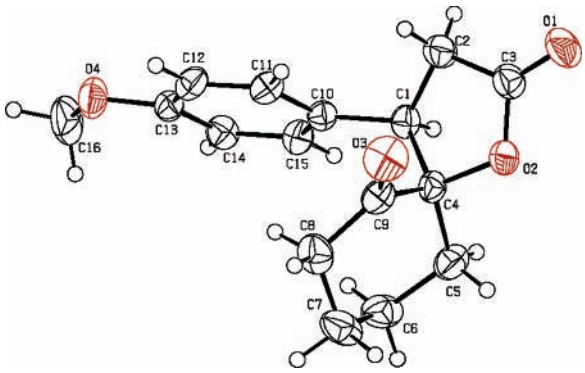
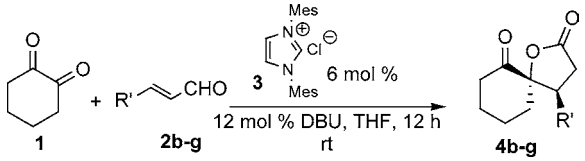


Figure 1. X-ray crystal structure of **4a**.

A number of enals were found to be suitable candidates for spirolactone synthesis, and the results are summarized in Table 1.

Table 1. Synthesis of Spirolactone Derivatives



entry	aldehyde	product	yield (%)
1	R′ = 4-chlorophenyl, **2b**	**4b**	60
2	R′ = phenyl, **2c**	**4c**	73
3	R′ = 4-methylphenyl, **2d**	**4d**	71
4	R′ = 4-fluorophenyl, **2e**	**4e**	74
5	R′ = 4-bromophenyl, **2f**	**4f**	65
6	R′ = 4-trifluorophenyl, **2g**	**4g**	60

It is noteworthy that spirocyclic γ-butyrolactones are a structural motif in a number of natural products such as Pathylactone A and Napalilactone.[18] In addition, they serve as key intermediates in the total synthesis of a variety of natural products.[19] Consequently, there has been considerable interest in developing efficient synthetic methods for these compounds.[20]

After the investigations described, we turned our attention to another important class of 1,2-dicarbonyl compounds, isatins, with a view to synthesize spiroannulated oxindole derivatives, the latter being an important structural unit of

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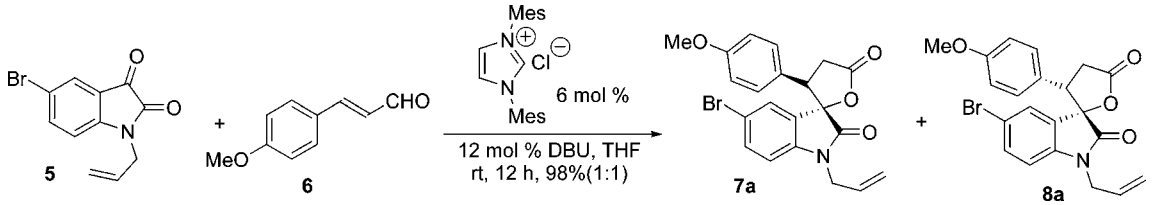
Scheme 2. Reaction of 4-Methoxycinnamaldehyde with Isatin



biologically active natural products, such as the mycotoxin triptoquivaline.[21]

In a prototype experiment, the reaction of 5-bromo-*N*-allylisatin with 4-methoxycinnamaldehyde in the presence of catalytic IMes (6 mol %) and DBU (12 mol %) yielded a separable diastereomeric mixture (1:1) of the spirobutyrolactone oxindole derivative in 98% total yield (Scheme 2).

The structure of **7a** was assigned on the basis of spectroscopic analysis; conclusive evidence for the assigned stereochemistry was obtained from single-crystal X-ray data (Figure 2).

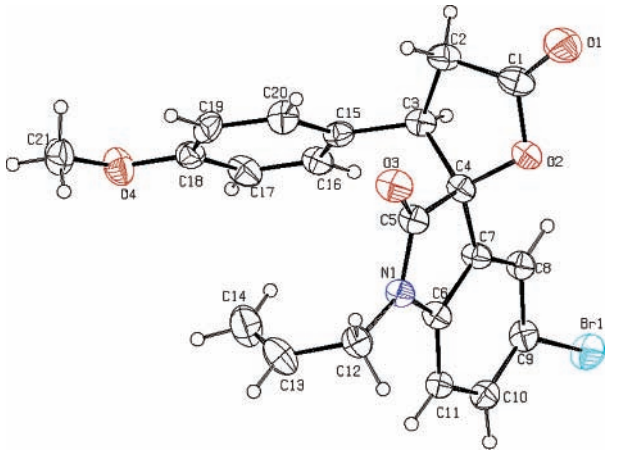
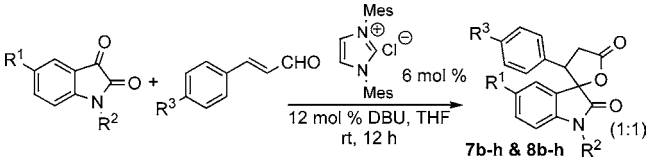


Figure 2. X-ray crystal structure of **7a**.

From our preliminary studies, it appears that the reaction is applicable to different isatins and enals (Table 2).

The reactions described here may be rationalized by invoking the mechanistic postulate of earlier workers[12,13] which entertains a catalytic cycle involving a homoenolate generated from cinnamaldehyde and nucleophilic carbene. This homoenolate then undergoes addition/cyclization with 1,2-diones to form the lactone ring and the regeneration of the catalyst.

Table 2. Synthesis of Spirooxindole Derivatives



entry	R^1	R^2	R^3	product	yield (%)
1	Br	allyl	H	**7b** & **8b**	98
2	Br	propyl	H	**7c** & **8c**	86
3	Br	propyl	OMe	**7d** & **8d**	98
4	H	methyl	H	**7e** & **8e**	92
5	H	methyl	OMe	**7f** & **8f**	85
6	H	propargyl	H	**7g** & **8g**	96
7	Br	methyl	H	**7h** & **8h**	90

In conclusion, we have successfully employed the organocatalyzed homoenolate chemistry for the synthesis of highly functionalized spiro butyrolactones. It is conceivable that the strategy may be applicable to the synthesis of natural products which display spiro γ-butyrolactone and spirobutyrolactone oxindole[19] motifs. In addition, the α-carbonyl spirolactones may serve as key intermediates in total synthesis.[22]

Acknowledgment. Dedicated with best wishes to Professor Ronald Breslow on the occasion of his 75th birthday. The authors thank the Council of Scientific and Industrial Research (CSIR) and the Department of Science and Technology (DST), New Delhi, for financial assistance.

Supporting Information Available: Synthetic procedures and spectroscopic characterization of selected compounds and single-crystal X-ray data of compounds **4a** and **7a.** This material is available free of charge via the Internet at http://pubs.acs.org.

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