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DABCO-Mediated [4+2] Annulation of But-3-yn-2-one and Activated Ketones: Facile Preparation of 2,3-Dihydropyran-4-one

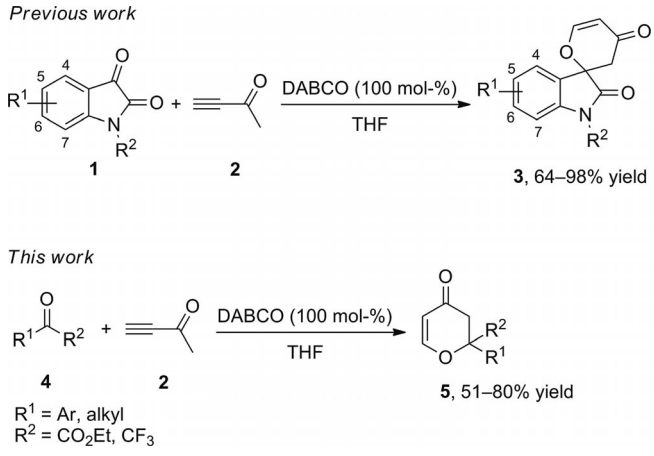
Zhong Lian,[a] Qian-Yi Zhao,[a] Yin Wei,[a] and Min Shi*[a]

Keywords: Ketones / Alkynes / Lewis bases / Organocatalysis / Annulation

We found that nitrogen-containing Lewis base mediated [4+2] annulation of but-3-yn-2-one with activated ketones could proceed efficiently to give the corresponding 2,3-dihydropyran-4-ones in moderate to good yields under mild conditions. The substrate scope has been carefully examined. Moreover, a plausible reaction mechanism for the [4+2] annulation of but-3-yn-2-one with activated ketones mediated by DABCO has been proposed on the basis of previous literature and our own investigations.

Introduction

2,3-Dihydropyran-4-ones are present in many natural products.[1] Their rich source of functionalities renders them versatile intermediates in the synthesis of a variety of biologically important compounds, such as carbohydrates,[2] antibiotics,[3] and toxins.[4] The syntheses of 2,3-dihydropyran-4-one have been well documented in the literature. A pioneering synthetic approach for such heterocycles was established through the hetero-Diels–Alder reaction of carbonyl compounds and activated dienes by Danishefsky and coworkers.[5] Later, many research papers and excellent reviews reported variations and improvements to that originally published synthetic method, which provide the basis for a number of synthetic strategies.[6] New strategies that have been recently developed include the tandem aldol reaction/conjugate addition[7] and the oxidative cyclization of α-hydroxyenones with a palladium(II) catalyst.[8] The addition of a variety of nucleophiles to unsaturated lactones that result from the reaction of Brassard's diene with aldehydes has also been employed to synthesize 2,3-dihydropyran-4-ones.[9] In 1999, Ramachandran and co-workers reported that DABCO (1,4-diazabicyclo[2.2.2]octane) catalyzed the self- and cross-condensation of but-3-yn-2-one.[10] In their report, but-3-yn-2-one was deprotonated by DABCO to produce the corresponding carbanion, and intermolecular condensation then took place. Inspired by those results, we have recently reported that nitrogen-containing Lewis base catalyzed [4+2] annulation of isatins **1** with but-3-yn-2-one (**2**) could proceed smoothly to give the corresponding spirocyclohexaneoxindoles **3** in good to excellent yields under mild reaction conditions (Scheme 1).[11] In this paper, we wish to disclose a novel nitrogen-containing Lewis base mediated [4+2] annulation of activated ketones **4** with but-3-yn-2-one (**2**) to produce the corresponding 2,3-dihydropyran-4-ones **5** in good yields under mild conditions (Scheme 1).[11]



Scheme 1. Nitrogen-containing Lewis base mediated [4+2] annulations.

Results and Discussion

The initial investigation involved the reaction of the activated ketone ethyl 2-oxo-2-phenylacetate (**4a**, 1.0 equiv.) and but-3-yn-2-one (**2**, 1.5 equiv.) in the presence of DABCO (20 mol-%) in tetrahydrofuran (THF) at room temperature (20 °C). We found that oxygen-atom-containing six-membered cyclic product ethyl 4-oxo-2-phenyl-3,4-dihydro-2*H*-pyran-2-carboxylate (**5a**) was obtained in 15% yield (Table 1, Entry 1). The structure of product **5a** was assigned on the basis of spectroscopic analyses. Its structure

[a] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032 China
Fax: +86-21-64166128
E-mail: mshi@mail.sioc.ac.cn

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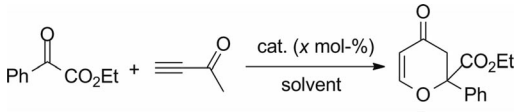
was further unambiguously determined by X-ray diffraction analysis of its analogue compound **5n**. The ORTEP drawing of **5n** is shown in Figure 1.[12] Pleasingly, increasing the amount of DABCO employed to 0.5 equiv. (50 mol-%) and 1.0 equiv. (100 mol-%) afforded product **5a** in 37 and 75% yield, respectively (Table 1, Entries 2 and 3). However, increasing the amount of DABCO further to 1.2 or 1.5 equiv. did not significantly improve the yield of product **5a** (Table 1, Entries 4 and 5). When the reaction was carried out by using **4a**/**2**/DABCO = 1:1:1 or 1:2:1 in THF at room temperature, it was found that corresponding annulation product **5a** was obtained in 62 and 75% yield, respectively (Table 1, Entries 6 and 7). Using other nitrogen- or phosphorus-containing Lewis bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine, 4-*N*,*N*-dimethylpyridine (DMAP), diisopropylethylamine (DIPEA), triphenylphosphane, methyldiphenylphosphane, and tributylphosphane did not further improve the yield of **5a** and no reactions occurred in most cases (Table 1, Entries 8–14), indicating that DABCO is the best promoter for this reaction. An examination of solvent effects revealed that THF is the solvent of choice for this novel [4+2] annulation reaction (Table 1, Entries 15–18).

Table 1. Optimization of the reaction conditions.[a]



4a **2** **5a**

Entry	**4a**/**2**	Catalyst	*x* [mol-%]	Solvent	Yield [%][b]
1	1:1.5	DABCO	20	THF	15
2	1:1.5	DABCO	50	THF	37
3	1:1.5	DABCO	100	THF	75
4	1:1.5	DABCO	120	THF	74
5	1:1.5	DABCO	150	THF	75
6	1:1	DABCO	100	THF	62
7	1:2	DABCO	100	THF	75
8	1:1.5	DMAP	100	THF	–
9	1:1.5	DBU	100	THF	trace
10	1:1.5	Et_3N	100	THF	35
11	1:1.5	DIPEA	100	THF	–
12	1:1.5	PPh_3	100	THF	–
13	1:1.5	PPh_2Me	100	THF	–
14	1:1.5	PBu_3	100	THF	–
15	1:1.5	DABCO	100	toluene	55
16	1:1.5	DABCO	100	DCM	72
17	1:1.5	DABCO	100	CH_3CN	61
18	1:1.5	DABCO	100	Et_2O	50

[a] Compound **4a** (0.1 mmol) and catalyst were dissolved in solvent (0.5 mL), and then compound **2** was added into the reaction solution. The resulting reaction mixture was stirred for 5 min. [b] Isolated yield.

Having identified the optimal reaction conditions, we next set out to examine the substrate scope of this [4+2] annulation mediated by DABCO by using various activated ketones **4** with different substituents on the R^1 and R^2 groups. The results are summarized in Table 2. The reactions proceeded efficiently to give the corresponding products **5b**–**i** in moderate to good yields regardless of whether

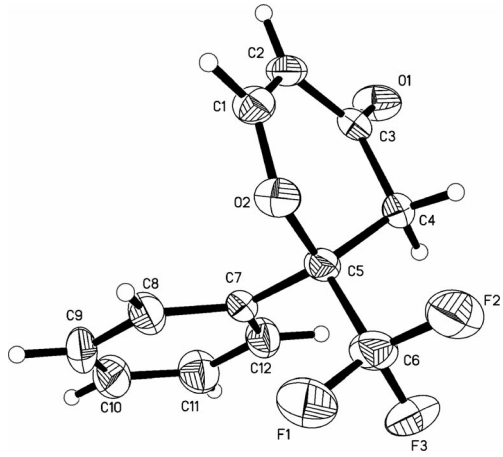
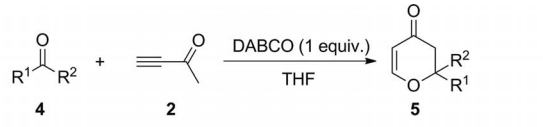


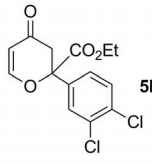
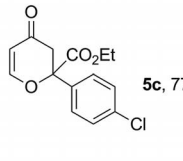
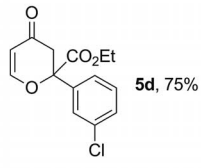
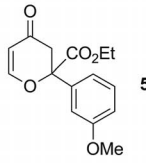
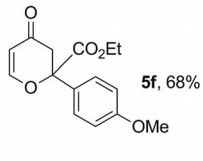
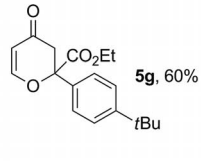
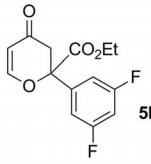
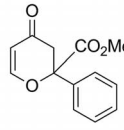
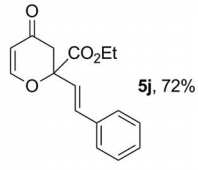
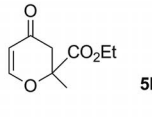
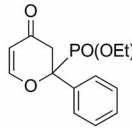
Figure 1. ORTEP drawing of **5n**.

electron-withdrawing or electron-donating groups were introduced on the benzene rings of the R^1 group, suggesting that the electronic properties of the substituents on the benzene rings did not have an impact on the outcome of the reactions (Table 2). It should be also noted that, in the

Table 2. Substrate scope of the [4+2] annulation.[a]



4 **2** **5**

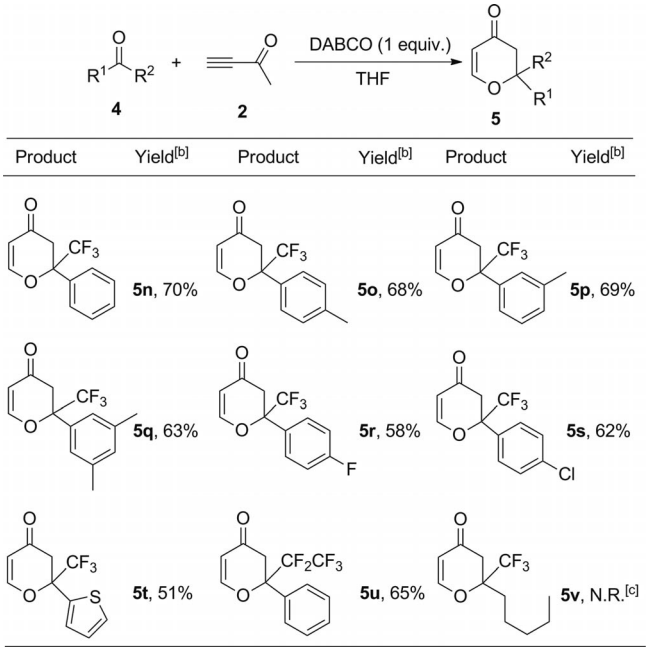
Product	Yield[b]	Product	Yield[b]	Product	Yield[b]
	**5b**, 80%		**5c**, 77%		**5d**, 75%
	**5e**, 65%		**5f**, 68%		**5g**, 60%
	**5h**, 69%		**5i**, 77%		**5j**, 72%
	**5k**, 70%		**5l**, N.R.[c]		**5m**, N.R.[c]

[a] Compound **4** (0.1 mmol) and DABCO were dissolved in solvent (0.5 mL), and then compound **2** was added into the reaction solution. The resulting reaction mixture was stirred for 5 min. [b] Isolated yield. [c] N.R. = No reaction.

case of other activated ketones **4j–k** bearing alkenyl and alkyl groups, the reactions also proceeded smoothly to produce the corresponding 2,3-dihydropyran-4-ones **5j** and **5k** in 72 and 70% yield, respectively (Table 2). We also found that other activated ketones such as phosphonate **4l** and amide **4m** did not give the corresponding products under the standard conditions.

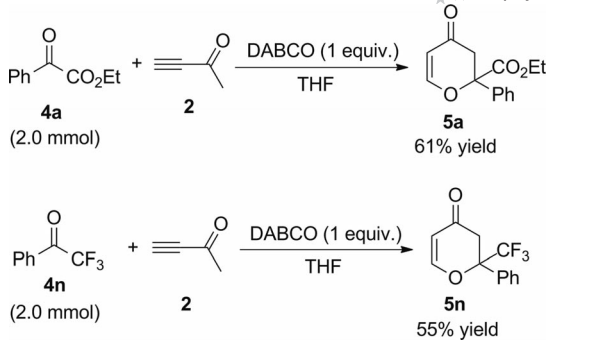
With the optimized reaction conditions in hand, we decided to further explore the substrate scope of this [4+2] annulation reaction. Activated ketones **4** bearing a trifluoromethyl group were treated with but-3-yn-2-one (**2**) under the standard conditions, and the results are shown in Table 3. We found that a wide range of activated ketones **4**, in which R^2 is a trifluoromethyl group, were suitable substrates in this reaction, affording desired 2,3-dihydropyran-4-ones **5n–s** in 58–70% yield regardless of the electronic properties of the aromatic R^1 groups on the benzene ring (Table 3). Extension of the substrate scope was also performed by using an activated ketone having a thiophene ring, giving desired product **5t** in 51% yield (Table 3). Moreover, increasing the fluorinated alkyl chain of R^2 did not hamper the reaction, giving desired product **5u** in 65% yield (Table 3). Notably, when R^2 was a pentyl group, the reaction did not give desired product **5v** (Table 3).

Table 3. Further examination of the substrate scope of the [4+2] annulation.[a]



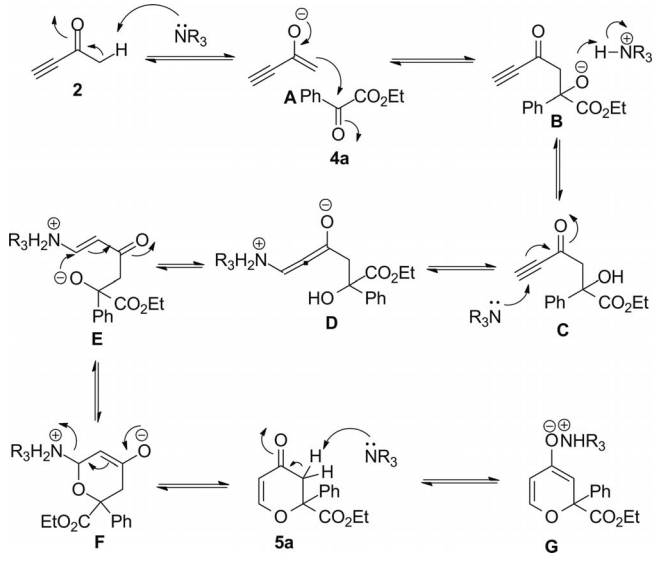
[a] Compound **4** (0.1 mmol) and DABCO were dissolved in solvent (0.5 mL), and then compound **2** was added into the reaction solution. The resulting reaction mixture was stirred for 5 min. [b] Isolated yield. [c] N.R. = No reaction.

To our delight, by increasing the reaction scale to 2.0 mmol, similar results could be obtained, affording the corresponding products **5a** and **5n** in a yield of 61 and 55%, respectively (Scheme 2).



Scheme 2. Enlarging the reaction scale of the [4+2] annulation reactions.

A plausible stepwise mechanism for the formation of **5a** is outlined in Scheme 3. Initially, DABCO deprotonates but-3-yn-2-one (**2**) to generate enolate intermediate **A**,[10,11] which undergoes nucleophilic addition to the carbonyl group of activated ketone **4a** to give intermediate **B**. Then, intermediate **B** undergoes protonation, and the following intermolecular Michael addition of DABCO to the alkynyl group in intermediate **C** gives intermediate **D**. This intermediate subsequently undergoes 1,5-hydrogen shift to produce intermediate **E**. The oxyanion of intermediate **E** attacks the alkenyl group to form six-membered cyclic intermediate **F**, which is followed by the release of DABCO to produce corresponding product **5a**. Notably, product **5a** may be deprotonated by DABCO to form ion pair **G**.



Scheme 3. A plausible stepwise mechanism for the formation of **5a**.

Conclusions

In summary, we have disclosed a facile synthetic protocol for the preparation of functionalized 2,3-dihydropyran-4-ones in moderate to good yields by nitrogen-containing Lewis base catalyzed annulations of activated ketones **4** with but-3-yn-2-one (**2**) under mild conditions. Moreover, a

plausible stepwise reaction mechanism for the [4+2] annulation of but-3-yn-2-one with activated ketones mediated by DABCO has been proposed on the basis of previous literature and our own investigations. Efforts are underway to elucidate the mechanistic details of this annulation and to explore some other interesting annulation reactions by using nitrogen-containing Lewis bases.

Experimental Section

General Procedure for the Formation of 5a: Under an argon atmosphere, activated ketone **4a** (0.1 mmol), but-3-yn-2-one (**2**, 0.15 mmol), DABCO (0.1 mmol), and THF (0.5 mL) were added into a Schlenk tube. The mixture was stirred at room temperature for 5 min, and the reaction was monitored by TLC. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel; PE/EtOAc, 2:1) to afford compound **5a** as a white solid in 75% yield.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectroscopic data, charts of the compounds shown in Table 1–3.

Acknowledgments

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[12] CCDC-868565 (for **5n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Empirical formula: $C_{12}H_9F_3O_2$; formula weight: 242.19; crystal color: colorless; crystal dimensions: $0.341 \times 0.201 \times 0.112$ mm; crystal system: monoclinic; lattice parameters: a = 12.356(2) Å, b = 11.2157(19) Å, c = 8.0006(14) Å, α = 90°, β = 90.451(4)°, γ = 90°, V = 1108.7(3) Å^3; space group: P_c; Z = 4; $D_{calcd.}$ = 1.451 g/cm^3; $F(000)$ = 496; final R indices [$I > 2\sigma(I)$] R_1 = 0.0547, wR_2 = 0.1670.

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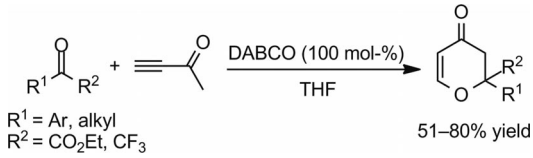
Organocatalysis



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