Organic LETTERS

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Atom-Economical Access to Highly Substituted Indenes and Furan-2-ones via Tandem Reaction of Diazo Compounds and Propargyl Alcohols

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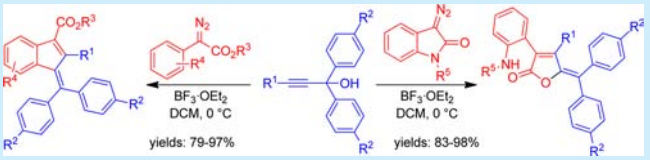
Supporting Information

ABSTRACT: A facile synthesis of highly substituted as well as conjugated indene/furanone systems via a $BF_3{\cdot}OEt_2$ catalyzed tandem reaction of α-diazo-esters/-amides and propargyl alcohols has been demonstrated under mild conditions. This method offers great potential for the synthesis of biologically active indene and furanone derivatives and their related polycyclic compounds.



Indenes[1] and furanones[2] are an important class of compounds that display a wide range of biological properties.[3] Many natural products[4] having these skeletons (Figure 1) have shown interesting properties in the field of medicine[5] and materials science.[6] Indene core structure containing metallocene complexes have been utilized in the polymerization process as catalysts.[7] Substituted indene and furanone derivatives serve as an important class of compounds that are used as building blocks.[8] The literature methods for the synthesis of indenes or furanones involve the cyclization of substituted allylic alcohols,[9] ring expansion of substituted cyclopropenes,[10] Lewis acid catalyzed Friedel–Crafts cyclization,[11] transition metals,[12] ruthenium-catalyzed carbonylative cyclization,[13] enyne methatesis,[14] and cross-coupling[15] reactions. Because of their importance in both chemical and pharmaceutical research, many methods involving transition-metal-catalyzed reactions for indenes and furanones have been reported. Although the above-mentioned methods are quite effective in synthesizing indenes and furanones, certain drawbacks are unavoidable in the preparation of substituted indenes and furanones, namely lengthy reaction sequences, strong acid conditions, heavy or rare earth metals, toxicity, low natural abundance, and expensiveness. These constitute severe drawbacks for industrial applications. The reaction of α-diazocarbonyl compounds with tertiary propargylic alcohols in the presence of a rhodium(II) catalyst was known to furnish[16] hydroxy allenes (Scheme 1a). In continuation of our research interest[17] on the chemistry of α-diazocarbonyl compounds, we herein describe a novel tandem reaction that can afford a variety of highly substituted indenes and furanones

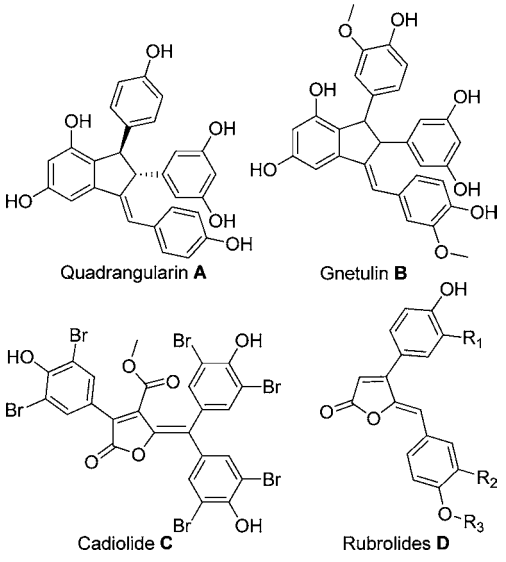
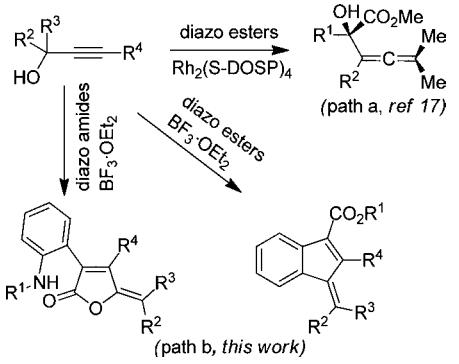


Figure 1. Selected examples of natural products.

Scheme 1. Reaction of Diazocarbonyl Compound and Propargyl Alcohol: (a) Insertion–Rearrangement; (b) Annulation



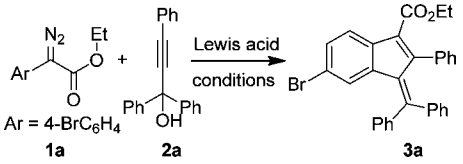
Received: July 4, 2014
Published: August 1, 2014

dx.doi.org/10.1021/ol501942y | Org. Lett. 2014, 16, 4248–4251

from α-diazo-esters/-amides and propargyl alcohols with 10 mol % of $BF_3{\cdot}OEt_2$ at 0 °C.

The required α-diazo-esters/-amides[18] **1** and propargyl alcohols[19] **2** were synthesized according to the literature methods. Initial study on the feasibility of a dichloromethane (DCM) solution containing an equimolar mixture of α-diazoester **1a** and propargyl alcohol **2a** in the presence of 10 mol % of $BF_3{\cdot}OEt_2$ at 0 °C for 10 min afforded highly substituted indene **3a** in 92% yield (Table 1, entry 1) in a tandem manner.

Table 1. Optimization of Reaction Conditions



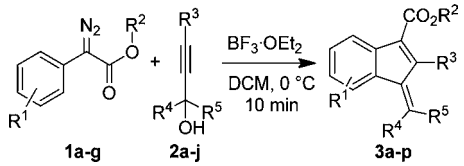
entry	Lewis acid	temp (°C)	time (min)	solvent	yield (%)[b]
1	$BF_3{\cdot}OEt_2$	0	10	DCM	92
2	$BF_3{\cdot}OEt_2$	0	10	DCE	79
3	$BF_3{\cdot}OEt_2$	0	10	hexane	83
4	$BF_3{\cdot}OEt_2$	0	15	THF	nd[c]
5	$Yb(OTf)_3$	30	15	DCM	64
6	$Sc(OTf)_3$	0	30	DCM	71
7	$FeCl_3$	0	30	DCM	68
8	$InCl_3$	0	30	DCM	66
9	CuOTf	30	30	DCM	25
10	TfOH	0	30	DCM	38
11	$AlCl_3$	0	60	DCM	nd[c]
12	$BF_3{\cdot}OEt_2$	0	10	DCM	84[d]

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (5 mL). [b]Isolated yield. [c]nd = no desired product. [d]Stoichiometric amount of $BF_3{\cdot}OEt_2$ used.

On the other hand, a low product yield was observed when the reaction was performed in 1,2-dichloroethane (DCE) or hexane (Table 1, entries 2 and 3). The reaction was also performed in tetrahydrofuran (THF) but did not yield the desired product **3a** (Table 1, entry 4). Similarly, a low yield of the product was observed when the reaction was performed in the presence of $Yb(OTf)_3$, $Sc(OTf)_3$, $FeCl_3$, or $InCl_3$ as a catalyst (Table 1, entries 5−8). Use of CuOTf or TfOH as a catalyst also provided **3a** in a very low yield (Table 1, entries 9 and 10). The reaction was found to result in a mixture of products when $AlCl_3$ was used as a catalyst (Table 1, entry 11). Further, experiments with a stoichiometric amount of $BF_3{\cdot}OEt_2$ did not improve the product yield compared to the catalytic reaction conditions (Table 1, entry 12). Thus, the optimized reaction conditions for the formation of **3a** were found to be 10 mol % of $BF_3{\cdot}OEt_2$ at 0 °C (Table 1, entry 1).

Encouraged by the above-mentioned result, we tested the substrate scope for the transformation, and the results are presented in Table 2. Reactions of α-diazoesters and propargyl alcohols bearing either an electron-donating or -withdrawing group on the arene gave the corresponding highly substituted and conjugated indene in excellent yields (Table 2, entries 1−6, 8, 10, 12−16). Substrates bearing an aliphatic moiety attached to the alkyne of propargylic alcohols smoothly furnished indenes **3g** and **3k** in good yield (Table 2, entries 7 and 11). The effect of the substituent at the *para*-position of phenyl acetylene was not noticeable in yielding product **3h** (Table 2, entry 8). A propargylic alcohol bearing a terminal alkyne unit was also examined under the above-mentioned conditions to afford indene **3i** in 79% yield (Table 2, entry 9). Employment of unsymmetrical propargyl alcohols also yielded product **3n** (Table 2, entry 14) in 96% yield. In general, the electron-donating/-withdrawing substituent on the starting substrates afforded the highly substituted indene derivatives in a tandem manner, and the results are presented in Table 2.

Table 2. Synthesis of Highly Substituted Indenes 3[a]



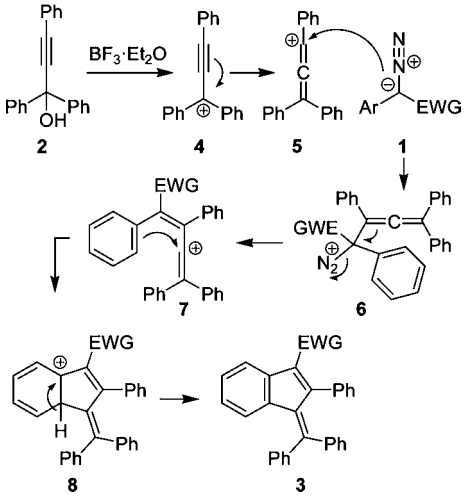
entry	R^1/R^2	$R^3/R^4/R^5$	product/yield (%)[b]
1	**1a** (4-Br/Et)	**2a** (Ph/Ph/Ph)	**3a**/92
2	**1b** (4-Br/propargyl)	**2a**	**3b**/89
3	**1c** (4-Cl/allyl)	**2a**	**3c**/88
4	**1d** (4-NO_2/*n*-butyl)	**2b** (Ph/*p*-tolyl/*p*-tolyl)	**3d**/90
5	**1e** (4-H/Me)	**2a**	**3e**/95
6	**1f** (4-CH_3/*n*-butyl)	**2a**	**3f**/97
7	**1g** (2-CH_3/Et)	**2c** (cyclopropyl/Ph/Ph)	**3g**/86
8	**1a**	**2d** (4-MeC_6H_4/Ph/Ph)	**3h**/90
9	**1a**	**2e** (H/Ph/Ph)	**3i**/79
10	**1b**	**2b**	**3j**/94
11	**1c**	**2f** (*n*-C_4H_9/Ph/Ph)	**3k**/83
12	**1c**	**2g** (Ph/4-ClC_6H_4/4-ClC_6H_4)	**3l**/90
13	**1d**	**2c**	**3m**/81
14	**1e**	**2h** (Ph/4-$OMeC_6H_4$/Ph)	**3n**/96
15	**1f**	**2g**	**3o**/93
16	**1g**	**2i** (Ph/4-FC_6H_4/4-FC_6H_4)	**3p**/91

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), solvent (5 mL). [b]Isolated yield refers to highly substituted indenes.

dx.doi.org/10.1021/ol501942y | *Org. Lett.* 2014, 16, 4248−4251

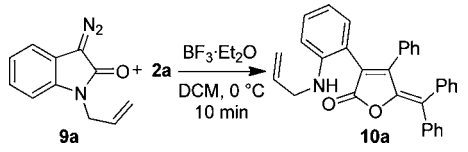
A proposed mechanism for the above tandem reaction is shown in Scheme 2. The propargylic alcohol **2** was converted to the allene carbocation intermediate **5** in the presence of $BF_3{\cdot}OEt_2$ via Meyer–Schuster rearrangement.[20] Subsequently, the carbocation **5** was trapped by nucleophilic attack of diazo compound **1** to produce the key intermediate aryl allene derived compound **6**. Meanwhile, elimination of nitrogen gas from **6** led to the vinylic cationic species **7**, which may undergo an electrocyclic ring closure of intermediate **7** (Nazarov cyclization), affording the cationic species of indene **8**, and the subsequent elimination of a proton led to the desired product **3**.

Scheme 2. Proposed Mechanism for Substituted Indenes 3



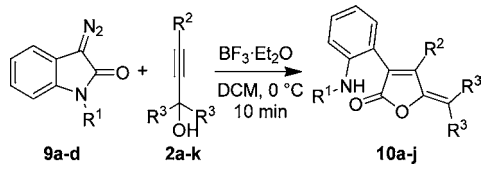
After studying the generality of the mechanism for the one-pot synthesis of highly substituted indene derivatives from phenyl α-diazoesters and tertiary propargylic alcohols, we next focused our attention on expanding the utility of this method using a variety of cyclic α-diazoamides. With this view, a solution containing an equimolar mixture of α-diazoamide **9a** and alcohol **2a** in the presence of 10 mol % of $BF_3{\cdot}OEt_2$ for 10 min in dry DCM furnished highly substituted furanone **10a** in 98% yield (Scheme 3) instead of yielding an indene derivative as described above.

Scheme 3. Synthesis of Highly Substituted Furanone 10a



Next, the scope of reactions was studied with a variety of reactants, and the results are summarized in Table 3. A similar reaction of α-diazoamides **9** and propargylic alcohols **2** furnished the corresponding furanones **10a–j** in a tandem manner. The alkynol bearing an electron-donating or -withdrawing group at the *para*-position of the aryl moiety gave the product in excellent yields. Similarly, propargyl alcohols having a hydrogen or an alkyl group on R^2 afforded furanone derivatives **10d,f,j** in comparable yields (Table 3, entries 4, 6, and 10). α-Diazoamide having a *tert*-butyloxycarbonyl group on the N atom was also examined for this transformation, but in vain.

Table 3. Synthesis of Functionalized Furanones 10a–j[a]

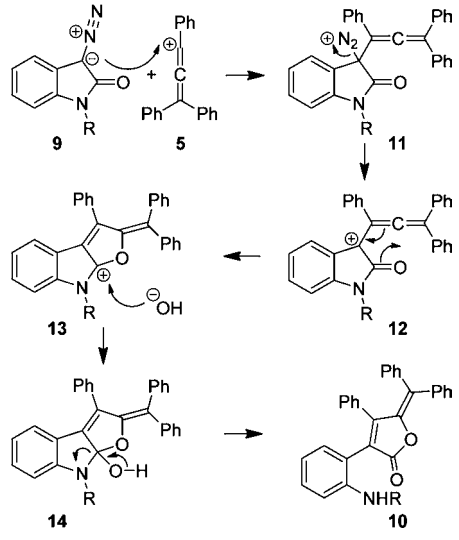


entry	R^1	R^2/R^3	product/yield (%)[b]
1	**9a** (allyl)	**2a**	**10a**/98
2	**9b** (benzyl)	**2a**	**10b**/94
3	**9b**	**2d**	**10c**/96
4	**9b**	**2e**	**10d**/88
5	**9c** (Me)	**2a**	**10e**/95
6	**9c**	**2f**	**10f**/83
7	**9c**	**2i**	**10g**/89
8	**9d** (Et)	**2b**	**10h**/98
9	**9d**	**2g**	**10i**/95
10	**9d**	**2j** (n-C_7H_{15}/C_6H_5)	**10j**/90

[a]Reaction conditions: **9a** (0.5 mmol), **2a** (0.5 mmol), solvent (5 mL). [b]Isolated yield refers to highly substituted furanones.

On the basis of the aforesaid experiments, a plausible mechanism is outlined in Scheme 4. A Lewis acid generates allene carbocation **5** *in situ* from propargyl alcohol, which was trapped by the nucleophilic addition on the diazo substituted carbon affording allene intermediate **11** (Scheme 4). The loss

Scheme 4. Proposed Mechanism for Furanones 10



of nitrogen on **11** may furnish cation **12**, which may undergo an electrocyclization process providing intermediate **13**. Nucleophilic addition of the hydroxyl group to the carbocation **13** cleaves the C–N bond vs the C–O bond in the tricyclic moiety **14**. The latter may undergo hydrogen abstraction affording more stable substituted furanones **10**. Interestingly, diazo esters afforded indenes whereas diazoamides yielded furanones involving the electrocyclization process.

In conclusion, a novel tandem reaction of α-diazocarbonyl compounds and propargyl alcohols catalyzed by $BF_3{\cdot}OEt_2$ is demonstrated to furnish highly substituted and conjugated

dx.doi.org/10.1021/ol501942y | Org. Lett. 2014, 16, 4248–4251

indene/furanone systems in excellent yields. Further studies on the application of this process in organic synthesis toward natural products are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.S. thanks the Council of Scientific and Industrial Research, New Delhi for a senior research fellowship. We thank the Department of Science and Technology, New Delhi for providing the 400 MHz NMR facility under the FIST program and supporting this research.

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