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DABCO-catalyzed synthesis of 3-bromo-/3-iodo-2*H*-pyrans from propargyl alcohols, dialkyl acetylene dicarboxylates, and *N*-bromo-/*N*-iodosuccinimides

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ABSTRACT

The DABCO-catalyzed reaction of propargyl alcohols with dialkyl acetylene dicarboxylates and *N*-bromo-/*N*-iodosuccinimides under mild conditions has been developed. The reactions give 3-bromo-/3-iodo-2*H*-pyrans in up to 98% yield.

Introduction

2*H*-Pyran and its analogues have been widely used in various areas such as materials, medicines, and agricultural chemicals.[1] As a precursor, 3-bromo-/3-iodo-2*H*-pyrans are important intermediates for the synthesis of 2*H*-pyran derivatives.[2] To the best of our knowledge, there are no examples of the synthesis of monocyclic 3-bromo-/3-iodo-2*H*-pyrans from propargyl alcohols, since they can undergo an electrocyclic ring-opening to give 1-oxatrienes in the presence of transition metal or at elevated temperatures.[3] Therefore, the development of attractive synthetic methods for the synthesis of monocyclic 3-bromo-/3-iodo-2*H*-pyrans is of great significance.

The groups of Toste[4] and Kirsch[3c,5] have reported a convenient method for the synthesis of monocyclic 2*H*-pyrans via Ag(I) or Au(I)-catalyzed propargyl-Claisen rearrangement (Scheme 1, Eq. 1). It should be noted that the transition metals are essential and the corresponding 2*H*-pyrans with bromine or iodine are not investigated. Herein, this study will focus on the reaction of propargyl alcohols, dialkyl acetylene dicarboxylates, and *N*-bromo-/*N*-iodosuccinimides in one pot, as well as the discovery of new *N*-bromo-/*N*-iodosuccinimides-induced electrophilic cyclization reactions[6] for the synthesis of 3-bromo-/3-iodo-2*H*-pyrans using organic base DABCO as a catalyst (Scheme 1, Eq. 2).

Results and discussions

In the course of our continuing investigation into the transformation of propargyl alcohols **1** to *O*-heterocycles, we found that treatment of the model substrate **1a** and **2a** (R^1 = Ph, R^2 = 4-IC_6H_4, R^3 = Me) with *N*-iodosuccinimide (NIS) and 5 mol % DABCO (1,4-diazabicyclo[2.2.2]octane) in dichloromethane for 12 h, a new style heterocycle, 3-iodo-2*H*-pyran, was obtained in 39% yield (Table 1, entry 1). Only DABCO among all the tested bases could selectively afford the 2*H*-pyran compound after 12 h (Table 1, entries 1–6). The reaction did not proceed in the absence of DABCO (Table 1, entry 7). Delightfully, the product was obtained in a satisfactory yield (88%, Table 1, entry 8) when the reaction was conducted in a 1:1:1.5 molar ratio (**1a**:**2a**:NIS) at 40 °C. Increasing the amount of NIS or lowering the temperature did not improve the product yield (Table 1, entries 9–11). The structure was unambiguously confirmed by single-crystal X-ray diffraction analysis of its derivative **3j**.[7]

With this result in hand, we explored the scope of this reaction, and the results are shown in Table 2.[8] When R^1 groups were the phenyl group, R^2 groups bearing different substituents: neutral groups (Table 2, entries 2–3), halogen groups (Table 2, entries 1 and 6–10), the cyano-group (Table 2, entry 11) were well tolerated,

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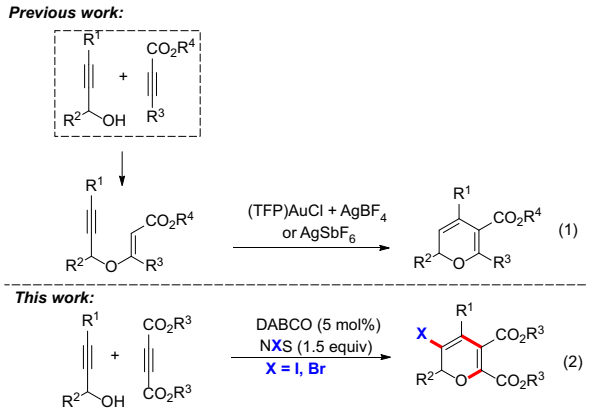
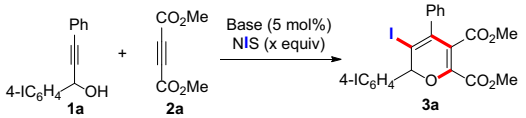


Scheme 1. Synthesis of 2*H*-pyran.

Table 1
Screening of the reaction conditions [a]



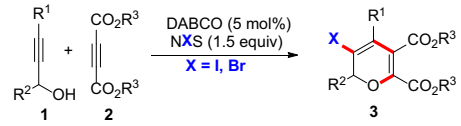
Entry	Base	*x*	Yield[b] (%)
1	DABCO	1	39
2	DBU	1	N.R.[c]
3	NMM	1	N.R.[c]
4	NEt_3	1	N.R.[c]
5	K_2CO_3	1	N.R.[c]
6	NaOAc	1	N.R.[c]
7	—	1	N.R.[c]
8	DABCO	1.5	88
9	DABCO	6	43
10	DABCO	8	49
11	DABCO	1.5	9[d]

[a] Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), base (5 mol %), NIS (*x* equiv), CH_2Cl_2 (2 mL), under argon atmosphere for 12 h, 40 °C.
[b] Isolated yields.
[c] N.R. = No reaction.
[d] 25 °C.

and the desired products were obtained with good to excellent yields. Naphthalene was also suitable for this process (Table 2, entries 4–5). Aryl R^1 groups also appeared quite tolerant with different substituents (Table 2, entries 12–13). When *N*-bromosuccinimide (NBS) was used instead of NIS at 40 °C, this reaction was not completive even with a longer reaction time (48 h). Therefore we raised the temperature to 50 °C and the products were obtained in satisfactory yields (Table 2, entries 14–19).

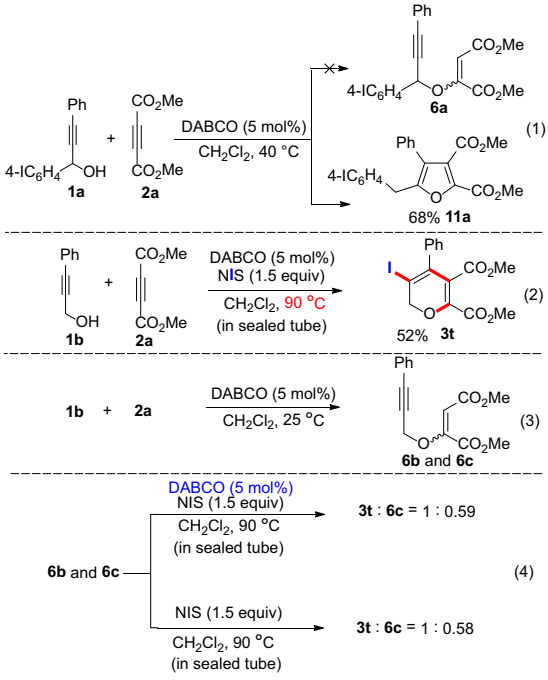
To elucidate the mechanism of this protocol, many experiments were carried out. The results are shown in Scheme 2. We found that the treatment of the model substrate **1a** and **2a** without NIS in dichloromethane for 12 h, dimethyl 5-(4-iodobenzyl)-4-phenylfuran-2,3-dicarboxylate **11a** instead of dimethyl 2-((1-(4-iodophenyl)-3-phenylprop-2-ynyl)oxy)maleate **6a**, was obtained in 68% yield (Scheme 2, Eq. 1). It is noteworthy that when R^2 was hydrogen atom, this cyclization could also proceed in a sealed tube (Scheme 2, Eq. 2). Fortunately, the addition products **6b** and **6c** were easily obtained from propargyl alcohol **1b** (Scheme 2, Eq. 3). When **6b** and **6c** were allowed to react under 90 °C, the corresponding products **3t** and **6c** were generated in a 1:0.59 ratio as determined by ^{1}H NMR analysis (Scheme 2, Eq. 4). In contrast, in the absence of DABCO, almost the same ratio of **3t** and **6c** were

Table 2
Scope of synthesis of 3-bromo-/3-iodo-2*H*-pyrans[a]



Entry	R^1	R^2	R^3	NXS	Yield[b] (%)
1	Ph	4-IC_6H_4	Me	NIS	88 (**3a**)
2	Ph	3-MeC_6H_4	Et	NIS	82 (**3b**)
3	Ph	4-MeC_6H_4	Et	NIS	63 (**3c**)
4	Ph	1-naphthyl	Et	NIS	85 (**3d**)
5	Ph	2-naphthyl	Et	NIS	32 (**3e**)
6	Ph	2-FC_6H_4	Et	NIS	49 (**3f**)
7	Ph	3-FC_6H_4	Et	NIS	88 (**3g**)
8	Ph	4-ClC_6H_4	Et	NIS	87 (**3h**)
9	Ph	2,3-$Cl_2C_6H_3$	Me	NIS	82 (**3i**)
10	Ph	2,3-$Cl_2C_6H_3$	Et	NIS	98 (**3j**)
11	Ph	4-CNC_6H_4	Et	NIS	89 (**3k**)
12	4-MeC_6H_4	Ph	Et	NIS	77 (**3l**)
13	4-ClC_6H_4	Ph	Et	NIS	93 (**3m**)
14	Ph	3-MeC_6H_4	Et	NBS	73 (**3n**)
15	Ph	1-naphthyl	Et	NBS	55 (**3o**)
16	Ph	3-FC_6H_4	Et	NBS	97 (**3p**)
17	Ph	2,3-$Cl_2C_6H_3$	Et	NBS	72 (**3q**)
18	4-ClC_6H_4	Ph	Et	NBS	96 (**3r**)
19	4-FC_6H_4	2,3-$Cl_2C_6H_3$	Et	NBS	92 (**3s**)

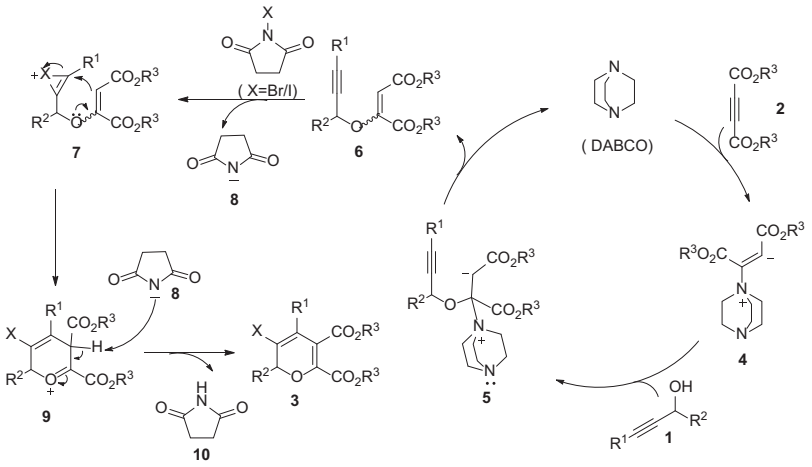
[a] Conditions: **1** (0.5 mmol), **2** (0.5 mmol), DABCO (5 mol %), NIS, or NBS (0.75 mmol), under Ar for 12 h, 40 °C for NIS (50 °C for NBS).
[b] Isolated yields.



Scheme 2. Mechanistic studies.

detected by ^{1}H NMR spectroscopy (Scheme 2, Eq. 4), indicating that DABCO was dispensable in the transformation of the intermediate **6** to the final product.

On the basis of these experimental results, a plausible reaction mechanism is depicted in Scheme 3. Initially, intermediate **4**[9] is formed from DABCO and dialkyl acetylene dicarboxylates **2**. Then, the zwitterionic **4** is attacked by propargyl alcohol **1** to form **5**. After release the DABCO catalyst, propargyl vinyl ether **6**[10] is abstracted. Intermediate **6** undergoes electrophilic cyclization with



Scheme 3. Proposed mechanism.

NIS (or NBS) to furnish **7** and succinimide anion **8**.[6] Subsequent cyclization of cation **7** generates cation **9**. The succinimide anion **8** traps a proton of **9** to form succinimide **10** and releases product **3**.

Conclusion

In summary, we have developed an efficient entry to 3-bromo-/3-iodo-2*H*-pyrans via an efficient *N*-bromo-/*N*-iodosuccinimide-induced organic base DABCO catalyzed electrophilic cyclization reaction of propargyl alcohols with dialkyl acetylene dicarboxylates in up to 98% yield. The mechanism involving the electrophilic cyclization step was established. The easily and commercially available starting materials, mild reaction conditions, combined with operational feasibility, make this method practical. This study provides a framework for further explorations of 3-bromo-/3-iodo-2*H*-pyrans derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.111.

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7. CCDC 988280 (**3j**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
8. (a) *General experimental procedure for the synthesis of 3-bromo-/3-iodo-2H-pyrans* ***3***: Propargyl alcohols **1** (0.5 mmol), dialkyl acetylene dicarboxylates **2** (0.5 mmol) and DABCO (0.025 mmol) were placed in a dried flask. NBS or NIS (0.75 mmol) in CH_2Cl_2 (2 mL) was added slowly. The resulting mixture was stirred at 40 °C (for NIS) or 50 °C (for NBS) under argon atmosphere until the consummation of raw material **1** detected by TLC. The solvent was evaporated under vacuum and the crude product was directly purified by silica gel flash column chromatography (eluent: 4:1 petroleum ether/ethyl acetate) to give the desired compound **3**.
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