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Synthesis and Utility of 2,2-Dimethyl-2*H*-pyrans: Dienes for Sequential Diels−Alder/Retro-Diels−Alder Reactions

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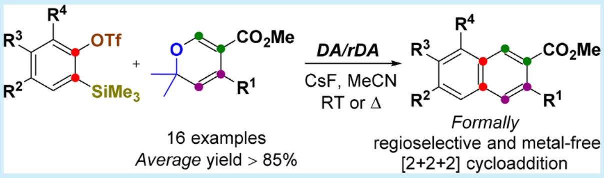
Supporting Information

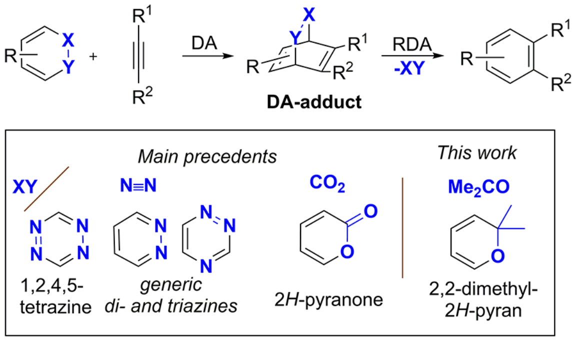
ABSTRACT: The practical use of 2,2-dimethyl-2*H*-pyrans as electron-rich dienes in sequential Diels−Alder/retro-Diels−Alder (DA/rDA) domino processes to generate aromatic platforms has been demonstrated. Different polysubstituted alkyl 2-naphthoates have been synthesized by the DA/rDA reaction of benzynes and 2,2-dimethyl-2*H*-pyrans. The use of other activated alkynes allows the access of substituted alkyl benzoate derivatives.



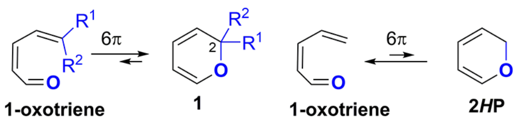
The sequential Diels−Alder/retro-Diels−Alder reaction (DA/rDAR; Scheme 1a) has found application in organic synthesis, with particular value in the construction of heteroaromatic platforms[1] and in chemical biology, especially in the field of bioorthogonal ligation.[2] Although the DA/rDAR manifolds based on 1,2,4,5-tetrazines,[1,2] triazines,[3] and 1,2-diazines[4] have received much attention, those based on 2*H*-pyran-2-ones[5] have also found use in organic synthesis to a lesser extent (Scheme 1a),[6] due to the harsher reaction conditions required, mainly when using alkenes as dienophiles.[7,8] An important drawback associated with these dienyl platforms is the synthetic difficulty to introduce functional diversity in their structures.[9] We[10] and others[11] have recently shown that 2,2-disubstituted-2*H*-pyrans **1** are convenient dienes for Diels−Alder reactions. In contrast to simple 2*H*-pyrans (2*HP*), which usually exist as an equilibrium mixture of monocycle and the linear 1-oxatriene (Scheme 1b),[12] the 2,2-disubstituted derivatives **1** constitute stable monocyclic entities amenable for isolation, storage, and handling. We envisioned that dienes based on the 2,2-dimethyl-2*H*-pyran unit, the most architecturally simple member of this series, could be suitable reactants for DA/rDAR manifolds if the acetone extrusion from the intermediate DA adduct (XY = Me_2CO; Scheme 1a) was spontaneous and substrate independent.[13] In terms of functional diversity, substituted members of the 2,2-dimethyl-2*H*-pyran series (i.e., **3**) would be easily accessible from the corresponding propargyl vinyl ethers **2** (PVEs) through the thermally driven all-pericyclic cascade reaction depicted in Scheme 1c.[10] The pericyclic manifold would deliver the 2*HP* derivatives **3** endowed with a variable substituent at C-4 and a fixed ester group (Z in Scheme 1c) at C-5. Interestingly, the reactivity of these 2,2-dimethyl-2*H*-pyrans (electron-rich dienes) should be complementary to that shown by aza-dienes and 2*H*-pyrones (electron-deficient dienes). We report herein the synthesis of these dienes and their use in domino DA/rDA manifolds designed to synthesize polysubstituted aromatic platforms.

Scheme 1. Synthesis and Use of 2,2-Dimethyl-2*H*-pyrans in Diels−Alder/Retro-Diels−Alder Manifolds

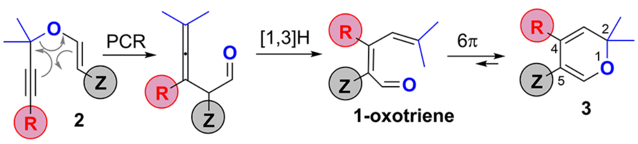
a) Sequential Diels-Alder/retro-Diels-Alder reaction (DA/DAR).



b) Stability of 2,2-dimethyl-2*H*-pyrans versus 2*H*-pyrans



c) Domino synthesis of 2,2-dimethyl-2*H*-pyrans



PCR = propargyl Claisen rearrangement; Z = ester group

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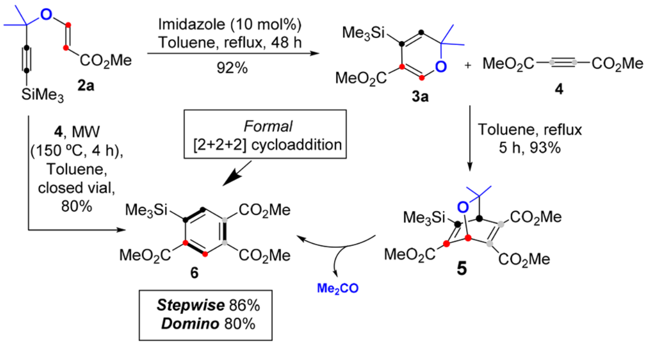
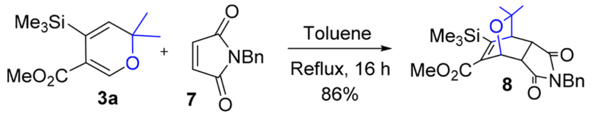
We began searching for the experimental conditions needed to transform PVE **2a** into the corresponding 2*H*P **3a**, arriving at a set of optimized reaction conditions which entailed imidazole as catalyst (10 mol %), refluxing toluene as the reaction medium, and 48 h as the reaction time (Scheme 2).

Scheme 2. Exploring the Use of 2,2-Dimethyl-2*H*-pyrans as Dienes in DA/rDA Manifolds



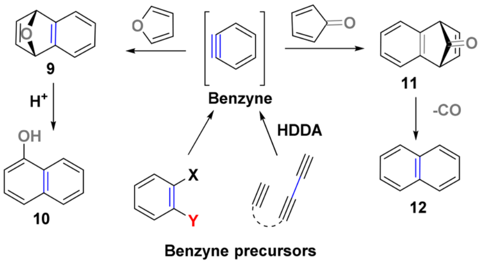
Under these conditions, **3a** could be obtained in 92% yield.[14] We then continued exploring the behavior of **3a** as a Diels–Alder diene with dimethyl acetylenedicarboxylate (**4**) (Scheme 2). The use of a reactive, electron-poor alkyne as dienophile was expected to favor both the cycloaddition reaction (electronic matching) and the acetone extrusion (rDA, aromatization) from the bicyclic DA adduct intermediate **5**. The heating of **3a** with **4** in toluene under reflux for 5 h delivered the 1,2,4-benzenetricarboxylate derivative **6**[15] in excellent yield (95%). Due to the orthogonal reactivity of the starting PVE **2a** and dienophile **4**, the telescoping synthesis was carried out with excellent yield (80%) (toluene, MW, 150 °C, 4 h). Formally, the whole process can be considered a regioselective and metal-free [2 + 2 + 2] cycloaddition reaction[16] of methyl propiolate, trimethylsilylacetylene, and dimethyl acetylenedicarboxylate. It should be noted that selective [2 + 2 + 2] cycloadditions of three different alkynes remain challenging in current organic synthesis.[16b] On the other hand, the reaction of **3a** with *N*-benzylmaleimide (**7**) (1.5 equiv, toluene, reflux, 16 h) delivered the corresponding DA adduct **8** in good yield (86%) (eq 1). As was expected,[17] the rDA reaction was not observed in this case because the acetone extrusion requires aromatization to proceed. Once the suitability of these dienes for DA/rDA reactions was shown, we next explored their utility in the synthesis of fused aromatic polycycles, specifically, in the synthesis of substituted alkyl 2-naphthoates, a valuable aromatic scaffold in material science.[18] The classical chemical methods for synthesizing substituted naphthoic acids, including the Kolbe–Schmitt carboxylation of naphthols and the alkali fusion of sulfonaphthoic acids, require harsh reaction conditions, multistep processes, and environmentally harmful chemicals.[19] In addition, they are accompanied by low regioselectivity, which ultimately translates to low yields.



(1)

Recently, a gold-catalyzed cyclization of aromatic *α*-hydroxyalkyl allenic esters was reported for accessing 2-naphthoate motifs adorned with different hydroxylation patterns.[20] The protocol imposes restrictive electronic requirements to the substituents adorning the final aromatic ring (electron-donating character). A more general and convenient route to these motifs relies on the DA reaction of in situ generated benzynes (highly reactive dienophiles) and rigid *cisoid* dienes such as furans, isobenzofurans, and cyclopentadienones among others (Scheme 3).[21] Both processes have been profusely explored[22] for accessing complex naphthol derivatives (furans/isobenzofurans) or reduced naphthalene derivatives (cyclopentadienones). Whereas the use of furans as dienes requires a subsequent acid treatment of the DA adduct intermediate **9** to generate the naphthol motif **10**, the in situ extrusion of CO from the DA adduct **11** directly affords the naphthalene scaffold **12**. Curiously, and despite the advances realized in aryne chemistry,[23] a few rigid dienes amenable to participate in DA/rDA manifolds have been explored. This scarcity prompted us to explore the viability of our DA/rDA manifold as a practical alternative and general protocol to gain access to these structural motifs (eq 2 in Scheme 5).

Scheme 3. DA Reaction of Benzynes with Furans and Cyclopentadiones To Generate Naphthalene Derivatives



Benzyne precursors

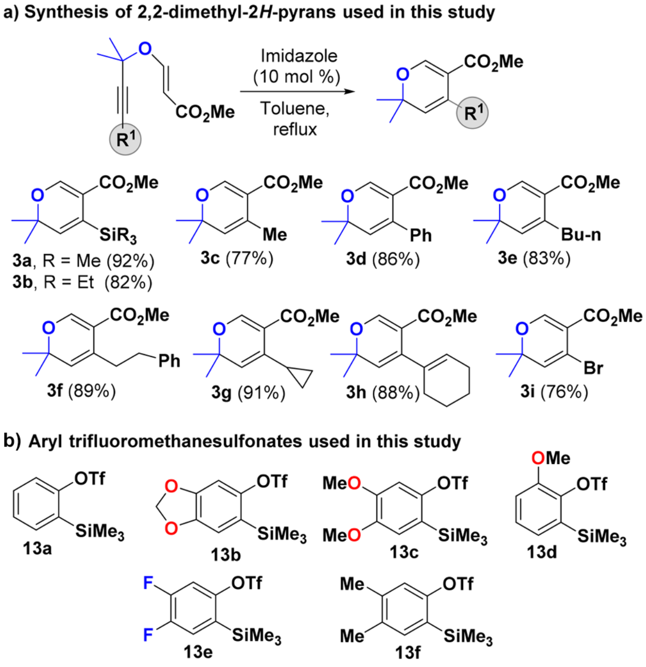
HDDA = *Hexadehydro-Diels-Alder*

[X,Y] = [H,LG] / [Hal,LG] / [SiMe$_3$,OTf] / [COO$^-$, N$_2^+$]

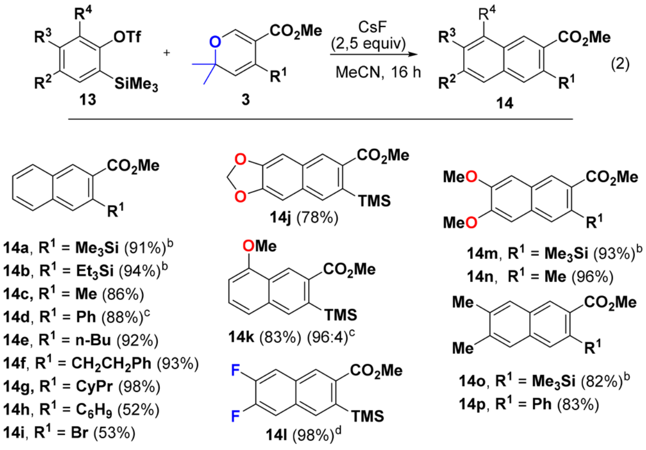
LG = *leaving group;* **Hal** = *halogen*

The viability of this protocol was established using the reaction of **3a** with the benzyne precursor **13a** and CsF as a model. After being stirred for 16 h at room temperature in acetonitrile, the reaction delivered the corresponding naphthoate derivative **14a** in an excellent 91% yield. Prompted by this result, we explored the scope of the reaction using a set of synthesized 2,2-dimethyl-2*H*-pyrans **3** and the aryl trifluoromethanesulfonates **13a–f** depicted in Scheme 4. In general, the reaction tolerated a wide range of substitution at the C-4 position of the pyranyl ring and the benzene ring of the aryne (Scheme 5, average yield: 85%). The substitution at C-4 spanned from cyclic and acyclic alkyl chains (**14c** and **14e–g**) to alkenyl (**14h**), phenyl (**14d**), silyl (**14a**,**b**), or bromide (**14i**). Although, in this last case, the yield decreased to a moderate 53%, it still remains synthetically competitive and highlights the chemical versatility and smoothness of the protocol. A similar decrease in yield (52%) was observed in the case of **14h**, which incorporates a conjugated alkene in its structure, amenable for participating in other competitive processes with the benzyne. As anticipated, and due to the known high reactivity of benzynes, the nature of the substitution pattern in the benzyne precursors has a very small influence on the overall yield of the reaction. Thus, the reaction tolerated both electron-donating groups (OMe, $-OCH_2O$, alkyl) and electron-withdrawing groups ($-F$) on the aromatic ring. Interestingly, the monosubstituted benzyne precursor **13d** afforded naphthoate derivative **14k** in 83% yield and a 96:4 ratio of regioisomers (the minor regioisomer is not

Scheme 4. (a) Synthesis of 2,2-Dimethyl-2*H*-pyrans 3 from PVEs 2 and (b) Set of Benzyne Precursors 13 Used in This Study



Scheme 5. Domino Synthesis of Alkyl 2-Naphthoates 14 from Benzyne Precursors 13 and 2,2-Dimethyl-2*H*-pyrans 3[a]



[a] General procedure: 2,2-dimethyl-2*H*-pyrane **3** (1 equiv), aryl trifluoromethanesulfonate **13** (1.25 equiv), CsF (2.5 equiv), MeCN (0.06 M), rt, 16 h. [b] Reflux. [c] Regioisomeric ratio. [d] **13** (1.5 equiv), CsF (3 equiv).

shown). The observed regioselectivity can be explained mainly from the polar effect of the methoxy substituent on the aryne (distortion effect) and the polarization of the diene system. This is in full accord with the regioselectivity predicted by the distortion model introduced by Houk.[24]

In summary, we have shown that 2,2-dimethyl-2*H*-pyrans **3** can participate in DA/rDA domino processes as the electron-rich diene component to generate polysubstituted aromatic platforms. Specifically, we have shown that the use of dimetyl acetylenedicarboxylate **4** as dienophile generates trimethyl 1,2,4-benzenetricarboxylate building blocks **6** armed with a substituent at the C-5 position of the ring (diversity point). The chemical outcome of this manifold formally corresponds with that of a regioselective [2 + 2 + 2] cycloaddition reaction of methyl propiolate, trimethylsilylacetylene, and dimethyl acetylenedicarboxylate. Moreover, we have shown that the reaction of these 2,2-dimethyl-2*H*-pyrans **3** with differently substituted benzyne precursors **13** generates the corresponding substituted alkyl-2-naphthoate derivatives **14** in excellent yields and regioselectivity (asymmetrically substituted benzyne). We believe that these electron-rich dienes will find practical use in organic synthesis, mainly in the domino synthesis of aromatic platforms hitherto inaccessible by current DA/rDA reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03558.

Detailed optimization, experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

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■ DEDICATION

Dedicated to Professor Víctor S. Martín on the occasion of his 65th birthday.

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