A strong-base induced [4+2] cycloaddition of homophthalic anhydrides with enolizable enones: a direct and efficient synthesis of *peri*-hydroxy aromatic compounds

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A direct and efficient synthesis of *peri*-hydroxy aromatic compounds *via* a strong-base induced [4+2] cycloaddition of homophthalic anhydrides with α -phenylsulfinyl enolizable enones has been accomplished.

In the past two decades, considerable effort has been devoted to the synthesis of biologically important polycyclic *peri*-hydroxy aromatic compounds which include anthracyclines,1 fredericamycin A,2 granaticin,3 bostrycin,4 olivin5 and other polycyclic antibiotics. Among the methods known for the construction of the key peri-hydroxy aromatic frameworks,6 the strong-base induced [4+2] cycloaddition reaction of homophthalic anhydrides to dienophiles7 continues to dominate, due to the generality and efficiency of the reaction as well as ready accessibility of the starting materials. An added advantage is the direct synthesis of peri-hydroxy compounds in a single step. The applicability of this methodology has already been realized in the total synthesis of a variety of natural products such as anthracyclines,11,8 galtamycinone9 and dynemicin A.10 However, all these examples utilize non-enolizable dienophiles such as quinone-type compounds or α,β -unsaturated esters.^{7b} On the other hand, the strong-base induced reaction of homophthalic anhydride with enolizable enones such as cyclohex-2-en-1-one or its β -substituted derivatives did not give any of the cycloaddition products^{7b} although in some cases the expected product was obtained in low yield.11 This is probably due to extensive enolization under the basic reaction condition, which might in turn retard the cycloaddition step.

Since the discovery of this reaction by us in 1982,^{7a} we have been engaged in developing its variants and utilizing this methodology for the synthesis of natural compounds. We have now extended this reaction to enolizable enones. We reasoned that the aforesaid problem could be readily overcome by the introduction of a suitable functional group at the α -position of the enone moiety which should be electron deficient in order to increase dienophilicity and should also behave as a leaving group, to provide directly the *peri*-hydroxy aromatic compounds.

A number of functional groups such as Br, SPh, S(O)Ph, SO₂Ph were considered and among them, the sulfinyl group, which fulfils the above-mentioned criteria, was found to be the substituent of choice. Here we report an efficient, strong-base induced [4+2] cycloaddition of various homophthalic anhydrides with α -sulfinyl substituted enones providing directly the *peri*-hydroxy aromatic compounds in moderate to good yields.

The homophthalic anhydrides **1a**–**d** were prepared according to the reported method.⁷ The strong-base induced reaction of homophthalic anhydride **1a** with 2-phenylsulfinylcyclopent-2-en-1-one **2a** was investigated in detail in order to optimize the reaction conditions. Similar to our earlier work,^{7d} we have found that NaH is more suitable than other bases (Bu'OK, LDA *etc.*). As can be seen from Table 1, among the various sets of reaction conditions tried, use of 1.1 equiv. of NaH in refluxing dioxane was adjudged the best, affording after acylation the *peri*-hydroxy compound as its acetate **3a** in good yield. In a typical experiment, to a slurry of NaH in dry dioxane was added a solution of homophtahlic anhydride **1a** in dioxane. The resulting slurry was stirred at room temperature for 30 min and then for 20 min each at 80 °C and 120 °C (bath temperature). Enone **2a** was then added and the reaction mixture was stirred for 20 min., cooled, quenched with aq. NH₄Cl and extracted with EtOAc. The crude reaction mixture, after evaporation of the solvent, was treated with Ac₂O and pyridine and left overnight at room temperature. Column chromatography afforded the *peri*-hydroxy aromatic compound as its acetate **3a**. Subsequently, all the reactions were performed using the same conditions, except for the final reaction time.

This base catalyzed [4+2] cycloaddition reaction was found to be general for a range of substituted homophthalic anhydrides **1a-d** as well as with different sulfinyl substituted enones **2a-e**, including that having an acetal functional group, affording the respective products in moderate to good yields (Table 2). Noteworthy is the success of the reaction with acyclic enone 2e, which is a rewarding result given the report that no reaction was observed between homophthalic anhydride and methyl but-2-enoate.^{11a} It is highly relevant that the reactions of homophthalic anhydrides 1a and 1b with cyclohex-2-en-1-one and cyclopent-2-en-1-one were not successful. The reactions under identical conditions resulted only in complex mixtures and no useful product could be isolated, indicating the possibility of a base-induced enolization in these cases. Thus, it is clearly evident that the sulfinvl group present at the α -position of the enone moiety plays an important role in directing the course of the reaction. Furthermore, the highlight of the reaction is the rapid syn-elimination of the phenylsulfinyl moiety under the reaction conditions, a unique characteristic of this functional group,^{7d} providing directly the *peri*-hydroxy aromatic compounds in a single step. The advantages of the sulfinyl group are emphasized by the fact that the strong-base induced reaction of homophthalic anhydride with 2-bromocyclohex-2-en-1-one was not successful. Reaction of 1a with 2-bromocyclohex-2-en-1-one, under identical conditions for 7 h, afforded after acylation acetate 3e in only 7% yield with the recovery of a large amount of unreacted bromocyclohexenone. Use of an additional equivalent of base (2.2 equiv.) in order to bring about the trans-elimination of HBr from a possible non-aromatized cycloadduct, did not lead to any significant improvement in the yield. The reaction afforded, after 3 h, the acetate 3e in only 10% yield.

Table 1 Reaction of homophthalic anhydride 1a with the enone 2a in the presence of NaH under various conditions

Entry	Solvent	T/°C	Time	Yield of $3a^{a}$ (%)		
1	THF	room temp.	25 h	20		
2	THF	reflux	15 min	41		
3	1,2-diethoxyethane	reflux	20 min	45		
4	1,4-dioxane	reflux	20 min	62		
a Isolate	d vields after column c	hromatography				

Table 2 NaH induced [4+2] cycloaddition reaction of various homophthalic anhydrides 1 with different sulfinyl substituted enones 2 in refluxing dioxane



Homophthalic and		Dienophile						Product		
1	R ¹	R ²	2	R ³		R ⁴	R ⁵	<i>t</i> /min	3	Yield (%) ^a
1a	Н	Н	2a		CH2		Н	20	3a	62
1b	Н	SPh	2a		CH2		Н	20	3b	58
1c	Н	OMe	2a		CH2		Н	20	3c	59
1d	OBn	Н	2a		-CH2-		Н	20	3d	56
1a	Н	Н	2b		-(CH ₂) ₂ -		Н	20	3e	70
1b	Н	SPh	2b		-(CH ₂) ₂ -		Н	20	3f	58
1c	Н	OMe	2b		-(CH ₂) ₂ -		Н	20	3g	62
1a	Н	Н	2c		-(CH ₂) ₃ -		Н	20	3h	60
1b	Н	SPh	2c		-(CH ₂) ₃ -		Н	20	3i	52
1a	Н	Н	2d		-(CH ₂) ₂ -		$(CH_2)_2 X^b$	20	3j	63
1b	Н	SPh	2d		-(CH ₂) ₂ -		$(CH_2)_2 X^b$	20	3k	57
1a	Н	Н	2e ^c	Ph		Н	Н	90	31	49
1b	Н	SPh	2e ^c	Ph		Н	Н	180	3m	48
1c	Н	OMe	2e ^c	Ph		Н	Н	210	3n	41
	1 1a 1b 1c 1d 1a 1b 1c 1a 1b 1a	I R ¹ 1a H 1a H 1b H 1c H 1d OBn 1a H 1b H 1c H 1b H 1b H 1b H 1b H 1c H 1a H 1b H 1c H	I R^1 R^2 IaHHIbHSPhIcHOMeIdOBnHIaHHIbHSPhIcHOMeIaHHIbHSPhIaHHIbHSPhIaHHIbHSPhIaHHIbHSPhIaHHIbHSPhIaHHIbHSPhIaHSPhIaHSPhIaHSPhIaHSPhIcHOMe	I R^1 R^2 2 IaHH2aIbHSPh2aIcHOMe2aIdOBnH2aIdOBnH2aIaHH2bIbHSPh2bIcHOMe2bIaHH2cIbHSPh2cIaHH2dIbHSPh2dIaHH2ecIbHSPh2dIaHH2ecIbHSPh2ecIbHSPh2ecIcHOMe2ecsafter column chromatography. b X = 1.3-dioxan-2-vl. c E: Z = 0	I R^1 R^2 I 1 R^1 R^2 I R^3 1aHH Za Ia 1bHSPh $2a$ Ia 1cHOMe $2a$ Ia 1dOBnH $2a$ Ia 1aHH $2b$ Ia 1bHSPh $2b$ Ia 1cHOMe $2b$ Ia 1aHH $2c$ Ia 1bHSPh $2c$ Ia 1bHSPh $2c$ Ia 1bHSPh $2d$ Ia 1bHSPh $2d$ Ia 1bHSPh $2d$ Ia 1aHH $2e^c$ Ph1bHSPh $2e^c$ Ph1cHOMe $2e^c$ Phsafter column chromatography. $^{b}X = 1.3$ -dioxan-2-yl. $^{c}E:Z = ca$. 6	I R ¹ R ² I 1 R ¹ R ² 2 R ³ 1a H H 2a -CH ₂ 1b H SPh 2a -CH ₂ 1c H OMe 2a -CH ₂ 1d OBn H 2a -CH ₂ 1d OBn H 2a -CH ₂ 1d OBn H 2a -CH ₂ 1d H H 2b -(CH ₂ 1a H H 2b -(CH ₂ 1b H SPh 2b -(CH ₂ 1a H H 2c -(CH ₂ 1b H SPh 2c -(CH ₂ 1a H H 2d -(CH ₂ 1b H SPh 2d -(CH ₂ 1a H H 2e ^c Ph 1b H SPh 2e ^c Ph 1b H SPh 2e ^c Ph	Image: constraint of the state of the transformation of transfor	Image: Image	I P R ¹ R ² Z R ³ R ⁴ R ⁵ t/min Ia H H 2a -CH ₂ H 20 Ib H SPh 2a -CH ₂ H 20 Ic H OMe 2a -CH ₂ H 20 Id OBn H 2a -CH ₂ H 20 Ia H B 2b -(CH ₂) ₂ H 20 Ia H SPh 2b -(CH ₂) ₂ H 20 Ia H M 2c -(CH ₂) ₂ H 20 Ib H SPh 2d -(CH ₂) ₂ (CH ₂) ₂ X ^b 20 Ia H SPh 2d -(CH ₂) ₂ (CH ₂) ₂ X ^b 20 <td>Image: constraint of the symbol is a stret column chromatography, b X = 1.3-dioxan-2-YL < E; Z = ca, 6:1 mixture. R^1 R^2 R^3 R^4 R^5 t/min 3 1a H H 2a -CH2- H 20 3a 1b H SPh 2a -CH2- H 20 3b 1c H OMe 2a -CH2- H 20 3c 1d OBn H 2a -CH2- H 20 3d 1a H H 2b -(CH2)- H 20 3c 1a H H 2b -(CH2)- H 20 3c 1b H SPh 2b -(CH2)2- H 20 3g 1a H H 2c -(CH2)2- H 20 3f 1b H SPh 2c -(CH2)3- H 20 3j 1b H SPh 2d -(CH2)2- (CH2)2X^k 20 3k</td>	Image: constraint of the symbol is a stret column chromatography, b X = 1.3-dioxan-2-YL < E; Z = ca, 6:1 mixture. R^1 R^2 R^3 R^4 R^5 t/min 3 1a H H 2a -CH2- H 20 3a 1b H SPh 2a -CH2- H 20 3b 1c H OMe 2a -CH2- H 20 3c 1d OBn H 2a -CH2- H 20 3d 1a H H 2b -(CH2)- H 20 3c 1a H H 2b -(CH2)- H 20 3c 1b H SPh 2b -(CH2)2- H 20 3g 1a H H 2c -(CH2)2- H 20 3f 1b H SPh 2c -(CH2)3- H 20 3j 1b H SPh 2d -(CH2)2- (CH2)2X ^k 20 3k

The generality and efficiency of the reaction, ready availability of the starting materials coupled with the unique activating as well as leaving ability of the sulfinyl group renders this method an attractive one for the synthesis of *peri*-hydroxy aromatic compounds using enolizable enones. The application of this methodology for the synthesis of natural products is in progress and will be reported in a forthcoming paper.

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