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] olivin[5] 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 dienophiles[7] 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,[1*i*,8] galtamycinone[9] and dynemicin A.[10] However, all these examples utilize non-enolizable dienophiles such as quinone-type compounds or α,β-unsaturated esters.[7*b*] 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[7*b*] 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,[7*a*] 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, SO_2Ph 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,[7*d*] we have found that NaH is more suitable than other bases (Bu^tOK, 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. NH_4Cl and extracted with EtOAc. The crude reaction mixture, after evaporation of the solvent, was treated with Ac_2O 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.

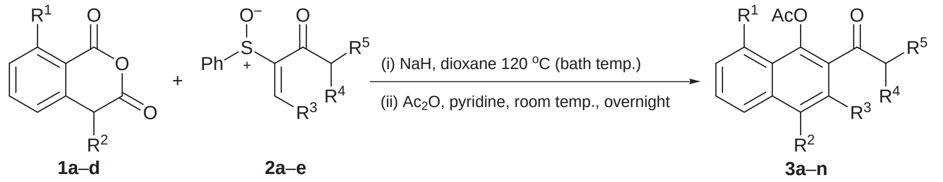
This base catalyzed [4+2] cycloaddition reaction was found to be general for a range of substituted homophthalic anhydrides **1a**–**d** as well as with different sulfinyl substituted enones **2a**–**e**, including that having an acetal functional group, affording the respective products in moderate 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.[11*a*] 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 sulfinyl 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,[7*d*] 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] Isolated yields after column chromatography

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



	Homophthalic anhydride			Dienophile					Product	
Entry	**1**	R^1	R^2	**2**	R^3	R^4	R^5	*t*/min	**3**	Yield (%)[a]
1	**1a**	H	H	**2a**	–CH$_2$–		H	20	**3a**	62
2	**1b**	H	SPh	**2a**	–CH$_2$–		H	20	**3b**	58
3	**1c**	H	OMe	**2a**	–CH$_2$–		H	20	**3c**	59
4	**1d**	OBn	H	**2a**	–CH$_2$–		H	20	**3d**	56
5	**1a**	H	H	**2b**	–(CH$_2$)$_2$–		H	20	**3e**	70
6	**1b**	H	SPh	**2b**	–(CH$_2$)$_2$–		H	20	**3f**	58
7	**1c**	H	OMe	**2b**	–(CH$_2$)$_2$–		H	20	**3g**	62
8	**1a**	H	H	**2c**	–(CH$_2$)$_3$–		H	20	**3h**	60
9	**1b**	H	SPh	**2c**	–(CH$_2$)$_3$–		H	20	**3i**	52
10	**1a**	H	H	**2d**	–(CH$_2$)$_2$–		$(CH_2)_2X$[b]	20	**3j**	63
11	**1b**	H	SPh	**2d**	–(CH$_2$)$_2$–		$(CH_2)_2X$[b]	20	**3k**	57
12	**1a**	H	H	**2e**[c]	Ph	H	H	90	**3l**	49
13	**1b**	H	SPh	**2e**[c]	Ph	H	H	180	**3m**	48
14	**1c**	H	OMe	**2e**[c]	Ph	H	H	210	**3n**	41

[a] Isolated yields after column chromatography. [b] X = 1,3-dioxan-2-yl. [c] *E* : *Z* = *ca.* 6 : 1 mixture.

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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Notes and references

1 (*a*) R. H. Thompson, *Naturally Occurring Quinones*, Academic Press, New York, 1971; (*b*) F. Arcamone, *Topics in Antibiotics Chemistry*, ed. P. G. Sammes, Halstead Press, New York, 1978, vol.2; (*c*) S. T. Crooke and S. D. Reich, *Anthracyclines*: *Current Status and New Developments*, Academic Press, New York, 1980; (*d*) F. Arcamone, *Med. Res. Rev*., 1984, **4**, 153; (*e*) P. T. Gallagher, *Contemp. Org. Synth*., 1996, **3**, 433; (*f*) S. Terashima, *J. Synth. Org. Chem. Jpn*., 1982, **40**, 20; (*g*) M. J. Broadhurst, C. H. Hassall and G. J. Thomas, *Chem. Ind*. (*London*), 1985, 106; (*h*) K. Krohn, *Angew. Chem., Int. Ed. Engl*., 1986, **25**, 790; (*i*) Y. Tamura and Y. Kita, *J. Synth. Org. Chem. Jpn*., 1988, **46**, 205; (*j*) K. Krohn, *Tetrahedron*, 1990, **46**, 291.

2 D. L. Boger, O. Hüter, K. Mbiya and M. Zhang, *J. Am. Chem. Soc*., 1995, **117**, 11839 and references cited therein.

3 K. Nomura, K. Okazaki, K. Hori and E. Yoshii, *J. Am. Chem. Soc*., 1987, **109**, 3402.

4 D. S. Larsen and R. J. Stoodley, *Tetrahedron*, 1990, **46**, 4711 and references cited therein.

5 W. R. Rousch, M. R. Michaelides, D. F. Tai, B. M. Lesur, W. K. M. Chong and D. J. Harris, *J. Am. Chem. Soc*., 1989, **111**, 2984 and references cited therein.

6 N. J. Broom and P. G. Sammes, *J. Chem. Soc., Chem. Commun*., 1978, 162; G. A. Kraus and H. Sugimoto, *Tetrahedron Lett*., 1978, 2263; F. M. Hauser and R. P. Rhee, *J. Org. Chem*., 1979, **101**, 178; J. H. Dodd and S. M. Weinreb, *Tetrahedron Lett*., 1979, 3593; J.-P. Gesson, J.-C. Jacquesy and B. Renoux, *Tetrahedron*, 1984, **40**, 4743; G. A. Kraus and B. S. Fulton, *Tetrahedron*, 1984, **40**, 4777; K. A. Parker and E. L. Tallman, *Tetrahedron*, 1984, **40**, 4781; D. L. Boger and I. C. Jacobson, *J. Org. Chem*., 1991, **56**, 2115.

7 (*a*) Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda and Y. Kita, *J. Org. Chem*., 1982, **47**, 4376; (*b*)Y. Tamura, M. Sasho, K. Nakagawa, T. Tsugoshi and Y. Kita, *J. Org. Chem*., 1984, **49**, 473; (*c*) Y. Tamura, M. Sasho, S. Akai, H. Kishimoto, J. Sekihachi and Y. Kita, *Chem. Pharm. Bull*., 1987, **35**, 1405; (*d*)Y. Kita, K. Iio, A. Okajima, Y. Takeda, K. Kawaguchi, B. A. Whelan and S. Akai, *Synlett*, 1998, 292 and references cited therein.

8 F. Matsuda, M. Kawasaki, M. Ohsaki, K. Yamada and S. Terashima *Tetrahedron*, 1988, **44**, 5745; J.-F. Lavallee, R. Rej, M. Courchesne, D. Nguyen and G. Attardo, *Tetrahedron Lett*., 1993, **34**, 3519; M. Kirihara and Y. Kita, *Heterocycles*, 1997, **46**, 705.

9 T. Matsumoto, H. Yamaguchi and K. Suzuki, *Synlett*, 1996, 433.

10 M. D. Shair, T. Y. Yoon, K. K. Mosny, T. C. Chou and S. J. Danishefsky, *J. Am. Chem. Soc*., 1996, **118**, 9509.

11 (*a*) Y. S. Rho, S. H. Park, Y. J. Kwon, J. H. Yoo and I. H. Cho, *Bull. Korean Chem. Soc*., 1996, **17**, 944; (*b*) D. Mal, N. K. Hazra, K. V. S. N. Murthy and G. Majumdar, *Synlett*, 1995, 1239; (*c*) A. P. Marchand, P. Annapurna, W. H. Watson and A. Nagl, *J. Chem. Soc., Chem. Commun*., 1989, 281.

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