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Aromatic Ring Annelation Using the 3-Carbomethoxy-1(3*H*)-isobenzofuranone and Methyl 2-carbomethoxybenzylcarboxylate

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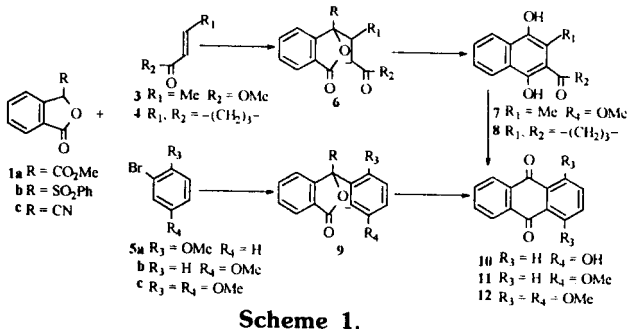
Phthalides are very useful in organic synthesis. Especially, by condensing their metallated intemediates with Michael acceptors such as α,β-unsaturated carbonyl compounds and arynes,[1] 3-phenylsulfonyl- and 3-cyano-1(3*H*)-isobenzofuranone have been widely used for the construction of anthraquinones, anthracyclines and other related compounds, which have biochemically important quinone moieties. These reactions are composed of Michael reaction followed by base-induced cyclization. Numerous phthalides which are cyclic form have been used as a Michael donor for the condensation with various α,β-unsaturated carbonyl compounds. For examples, 3-phenylsulfonyl-1(3*H*)-isobenzofuranone,[2] 3-cyano-1(3*H*)-isobenzofuranone,[3] and unvised phthalides[4] were employed. Various *o*-substituted benzyl derivatives which are open chained form have been also used as a Michael donor. For examples, methyl 2-carbomethoxybenzylcarboxylate,[5] 2-carboethoxybenzyl phenyl sulfoxide,[2] methyl 2-tosylmethylnicotinate[6] and 2-carbomethoxy toluene derivatives[7] were respectively utilized. Among those Michael donors, 3-cyano-1(3*H*)-isobenzofuranone was used to accomplish the quinone moiety with arynes by Khanapure.[8] Jung[9] explained the orientation of arynes generated *in situ* from haloarene with base. Besides, there are many examples to show the reactions of arynes with other donors.[10]

Referring to the series of those papers, we have been interested in whether phthalides and methyl 2-methylbenzoate substituted at the benzylic position with carbomethoxy group could serve as a Michael donor or not. The calculation of the withdrawing force of substituents[11] made us find out some differences in cyanides, phenyl sulfones, and recently reported dimethyl phthalide 3-phosphonate[12] (Table 1). Nevertheless, in the reaction of phthalide (**1a**) and methyl 2-methylbenzoate (**2a**) substituted at the benzylic position with carbomethoxy group, we obtain a similar reactivity that we did with various α,β-unsaturated carbonyl compounds and arynes. So herein we would like to report the results.

Results and Discussion

To synthesize the anthracycline derivatives, we have carried out the Michael reaction by three kinds of phthalide sulfone (7-methoxy, 4-methoxy- and unvised phthalide sulfone).[13] However, these three phthalides did not show any difference in their reactivities whether it had methoxy group on aromatic ring or not. So we tried the reaction with unvised phthalides **1a-c** and carboxylates **2a-c**. 3-Carbomethoxy-1(3*H*)-isobenzofuranone (**1a**), the new donor was obtained by the reaction of phthalide (1.0 g, 7.45 mmol) with methyl chloroformate (0.18 mL, 10.4 mmol) in the presence of *t*-BuOK (11.9 mL, 11.9 mmol, 1.0 M solution in THF) in 85% yield (mp 174-175 C) and **1b**, **1c** was prepared as reported[2,3] Methyl 2-carbomethoxybenzylcarboxylate (**2a**), 2-carbomethoxybenzyl phenyl sulfone (**2b**) and 2-carbomethoxy benzyl cyanide (**2c**) were prepared from methyl 2-methylbenzoate by the method 1. Schemes 1 and 2 show the reactions of two types of Michael donor (**1** and **2**) with two types of Michael acceptor (**3**, **4** and **5**).

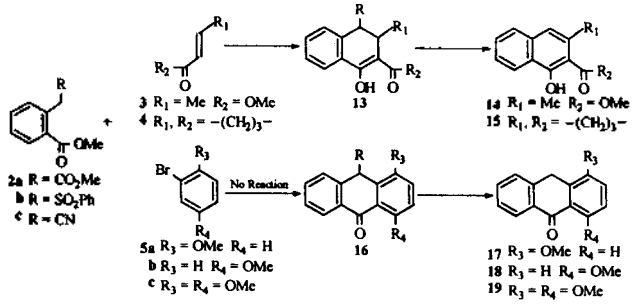
The reaction of **1a** with α,β-unsaturated carbonyl compounds (**3**, and **4**) was carried out under the method A (LDA/THF)[2,3] and the B (*t*-BuOLi/THF).[13] Consequently, the method B showed the better yield than the method A (Table 2). The other donors (**1b** and **1c**) were carried out under the same condition, and method B also showed the better



Scheme 1.

Table 1. Predicted Charge Densities for Benzylic Anions of the Donors **1**, **2** by PM3 and AM1

	R	HH	COOMe	SO_2Ph	CN	$PO(OMe)_2$	Tos	SOPh
Donor 1	AM1	−0.2865	−0.3256	−1.0601	−0.2257	−1.0682	−0.1022	−0.5073
	PM3	−0.3047	−0.3642	−0.7971	−0.2307	−0.7007	−0.0720	−0.4657
Donor 2	AM1	−0.3922	−0.4908	−1.0068	−0.3835	−1.3134	−0.3017	−0.6460
	PM3	−0.4602	−0.5666	−0.8217	−0.4185	−9522	−0.3604	−0.6267



Scheme 2.

yield than in LDA (Method A) or *t*-BuOK/DMSO.[14,15] However, three donors **1a-c** showed the almost same yield in the reaction with **3** and **4** under the method B.

It is supposed that the mechanism in the reaction of **1a** with α,β-unsaturated carbonyl compound **3** and **4** would be almost the same as that of **1b**[2] or **1c**.[3] Through those procedures, **7** was obtained easily from the reaction of **1** with **3**. The reaction of **1** with **4** made **8**, which was readily oxidized to the corresponding anthraquinone **10** in the air.[13,14] For the reaction of **1c** and bromoarene **5**, Khanapure[8] reported that *o*- and *m*-haloanisole could be reacted with **1c** in LDA respectively and Jung[9] reported that only *m*-haloanisole could be performed. Nevertheless, in our experiment, the new donor **1a** which had carbomethoxy group reacted with **5b**, **5c** under the method A, but *o*-bromoanisole (**5a**) what is like Jung's result, and that **1b**, **1c** also showed the same result as **1a** in LDA. However, in the method B, the result was proved completely different from that of the method A. It seems that three kinds of donor **1a-c** were not proceeded with any bromoarene **5a-c** in the presence of *t*-BuOLi.

In the reaction with benzyl carboxylate derivatives which are open chained form, Schmid[5] first reported the condensation of **2a** with **3** in the NaOMe to yield compound **13** (53%). So, Two kinds of base (Method A, B) were applied to Scheme 2. Compound **14** was obtained from the reaction of **2a** with **3** in LDA followed by the acidification of **13** with no purification, and the reaction of **2a** with **4** made **15** by the same method. The other donors, **2b** and **2c** made the results as shown in Table 2 by the reaction with **3** and **4**. In the method B, almost the same result was obtained by the reaction of **2a-c** and **3**, **4** respectively. Hauser and co-workers[2] could not obtain the **15** from the reaction of 2-carboethoxy phenyl sulfoxide with **4** in LDA. In contrast, we were able to prepare **15** from **2b** and **4** by the two methods. In the respective reaction of **2a** and bromoarenes **5a-c**, all the anisoles which had halogen in any position did not proceed. Furthermore, **2b** and **2c** did not react with **5a-c** under the two conditions, either. These suggest that the reactivity of **1** in the reaction with **5** is better than that of **2** between **2** types of donor.

In conclusion, the new Michael donor **1a** can produce the same reaction with Michael acceptor like as **1b** and **1c**. **2a-c** can react with α,β-unsaturated carbonyl compound **3** and **4**, but not with haloarenes **5a-c**. The reactivity of donor **1** composed of lactone ring is better than that of the open chained type donor **2** in the reaction with all of the Michael acceptors.

Experimental

All reagents and solvents were dried and purified according to the conventional procedures immediately before use. Melting points were determined on a Büchi 510 Apparatus and are uncorrected. GC/MS spectra were taken with a Nermag model R10-10C spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JMN-EX 400 MHz apparatus with TMS as the internal standard.

General Procedure for the Reaction of Michael Acceptors 3, 4 with Michael Donors 1, 2; (Method B).

Table 2. Yield(%) on Condensations of Michael Donors (**1a-c**, **2a-c**) with Michael Acceptors (**3**, **4**, **5a-c**) in Two Kinds of Base Condition

Donor	**1a**					**1b**					**1c**				
Acceptor	**3**	**4**	**5a**	**5b**	**5c**	**3**	**4**	**5a**	**5b**	**5c**	**3**	**4**	**5a**	**5b**	**5c**
Method A (LDA)[a,b]	78	74	–	35	70	72 (70)[e]	71 (69)[e]	–	40	70	76 (85)[b]	70 (42)[e]	– (35)[g]	43 (40)[g]	80 (75)[g]
Method B (*t*-BuOLi)[13]	93	90	–	–	–	92	91	–	–	–	85 (66)[f]	79 (60)[f]	–	–	–
Product	**7**	**10**	–	**11**	**12**	**7**	**10**	–	**11**	**12**	**7**	**10**	**11**	**11**	**12**
Donor	**2a**					**2b**					**2c**				
Acceptor	**3**	**4**	**5a**	**5b**	**5c**	**3**	**4**	**5a**	**5b**	**5c**	**3**	**4**	**5a**	**5b**	**5c**
Method A (LDA)[a,b]	62 (53)[e]	35	–	–	–	58 (44)[e]	31 (–)[e]	–	–	–	55	27	–	–	–
Method B (*t*-BuOLi)[13]	66	38	–	–	–	67	35	–	–	–	62	31	–	–	–
Product	**14**	**15**	–	–	–	**14**	**15**	–	–	–	**14**	**15**	–	–	–

[a] Acceptor (**3**) is ethylcrotonate, and Donor (**2b**) is 2-carboethoxybenzyl phenyl sulfoxide.[2] [b] Acceptor (**3**) is 3-penten-2-one or ethylcrotonate.[3] [c] Acceptor (**4**) is naphthalenone derivatives (two steps).[16] [d] Acceptor (**3**) is methyl vinyl ketone, base is *t*-BuOK/DMSO.[15] [e] Base is *t*-BuOK/DMSO[14] insted of *t*-BuOLi/THF. [f] Base is sodium methoxide.[5]

To a magnetically stirred cold (−78 ℃) solution of lithium *tert*-butoxide (3.0 mmol) prepared from *n*-butyllithium (1.87 mL, 3.0 mmol, 1.6 M solution in hexanes) and *tert*-butyl alcohol (0.28 mL, 3.0 mmol), Michael donor (1.0 mmol) was added as a slurry in THF (10 mL). The yellow anion solution, still at −78 ℃, was stirred 1 h and then Michael acceptor (1.0 mmol) in THF (5 mL) was added. The reaction was continued at −78 ℃ for 1 h at which point the cooling bath was removed and reaction was allowed to stand at rt overnight and was quenched by the addition of 3 N HCl. After standard assay work-up, the crude product was carried column chromatography (hexane : CH_2Cl_2, 1 : 9) to give **7**, **10**, **14**, **15** respectively.

Method A. All the procedures and conditions are the same as the method B except using LDA (3.0 mmol) instead of *t*-BuOLi.

Methyl 3-methyl-1,4-dihydroxy-2-naphthoate (7). light brown syrup; ^{1}H NMR ($CDCl_3$) δ 12.03 (s, 1H, OH), 8.01-8.10 (m, 2H), 7.59-7.63 (m, 2H), 3.99 (s, 3H, OCH_3), 2.50 (s, 3H, $PhCH_3$).

1-Hydroxyanthraquinone (10). **8** was prepared from **1** and **4**, and readily oxidized to **10**: yellow crystal; mp 177-8 ℃; ^{1}H NMR ($CDCl_3$) δ 12.62 (s, 1H, OH), 8.29-8.36 (m, 2H), 7.80-7.87 (m, 3H), 7.69 (t, 1H, J=8.06 Hz), 7.49-7.56 (m, 1H), 7.33 (dd, 1H, J=7.33, 1.47 Hz).

Methyl 1-hydroxy-3-methyl-2-naphthoate (14). light yellow syrup; ^{1}H NMR ($CDCl_3$) δ 11.90 (s, 1H, OH), 7.64-7.67 (m, 1H), 7.43-7.52 (m, 4H), 4.11 (s, 3H, $PhCH_3$), 3.84 (s, 3H, OCH_3); MS, m/z 216 (M^+).

10-Hydroxy-1,2,3,4-tetrahydroanthracen-1-one (15). orange crystal; mp 77-78 ℃; ^{1}H NMR ($CDCl_3$) δ 14.00 (s, 1H, OH), 8.10 (d, 1H, J=7.81 Hz), 7.44 (d, 1H, J=7.81 Hz), 7.39 (dd, 1H, J=7.81, 6.83 Hz), 7.25 (t, 1H, J=6.84 Hz), 2.82 (dd, 2H, J=5.86, 6.84 Hz), 2.56 (dd, 2H, J=5.86, 6.84 Hz), 1.93 (ddd, 2H, J=12.69, 6.84, 5.86 Hz); ^{13}C NMR δ 205.1, 163.3, 138.3, 137.4, 130.3, 126.8, 124.9, 124.4, 123.9, 116.3, 111.5, 39.0, 30.2, 23.0; Ms, m/z 212 (M^+).

General Procedure for the Reaction of bromoarenes 5a-c with Michael Donors 1, 2; (Method A). In a flame-dried flask flushed with nitrogen, LDA (3.0 mmol) was prepared by adding diisopropylamine (0.39 mL, 3.0 mmol) into a −78 ℃ solution of *n*-BuLi (1.87 mL, 3.0 mmol, 1.6 M solution in hexanes) in THF (10 mL) under a nitrogen atmosphere. After solution was stirred for 10 min, the appropriate Michael donor (1.0 mmol) in THF (10 mL) was added dropwise over 20 min. The reaction mixture was stirred at −78 ℃ for 10 min and then allowed to warm to −40 ℃. The reaction mixture was stirred further and allowed to warm to room temperature. The dark reddish brown solution was then quenched with saturated aqueous ammonium chloride solution, THF was evaporated under the reduced pressure, and the residue was extracted with methylene chloride. The combined extracts were washed with brine, dried ($MgSO_4$).

Method B. All the procedures and conditions are the same as the method A except using *t*-BuOLi (3.0 mmol) instead of LDA.

1-Methoxyanthraquinone (11). yellow crystal; mp 168-169 ℃; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, 1H, J=7.33, 1.47 Hz), 8.24 (d, 1H, J=8.06 Hz), 7.97 (d, 1H, J=7.32 Hz), 7.71-7.80 (m, 3H), 4.06 (s, 3H, OCH_3); MS, m/z 238 (M^+).

1,4-Dimethoxyanthraquinone (12). orange crystal; mp 160-162 ℃ (lit.[a] mp 165-166 ℃); ^{1}H NMR ($CDCl_3$) δ 8.17 (dd, 2H, J=5.86, 2.93 Hz), 7.71 (dd, 2H, J=5.86, 2.93 Hz), 7.35 (s, 2H), 4.00 (s, 6H, $OCH_3\times2$); ^{13}C NMR δ 183.5, 154.1, 134.2, 133.3, 126.4, 123.0, 120.2, 57.0; MS, m/z 268 (M^+).

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