Claisen Rearrangement of Allyloxyanthraquinones with Silver/Potassium Iodide in Acetic Acid as a New and Efficient Reagent

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Introduction

Functionalized anthraquinones have received much attention in recent years due to their industrial applications (e.g., textile dyestuff)[1] and their use as antiinflammatory agents[2] in the treatment of rheumatoid arthritis and as functional starting units in total synthesis of anthracycline antibiotics as anticancer drugs.[3] Yet the functionalization has been restricted to a narrow choice of chemical transformations. This is largely due to inertness of anthraquinone moieties to common electrophilic substitution reactions. Reductive Claisen rearrangement of allyloxyanthraquinones[3,4] has become a standard method for the introduction of alkyl groups onto the nucleus of anthraquinones.[5,6] Reduction of the quinone functionality with sodium dithionite in a mixture of *N*,*N*-dimethylformamide and water (1:1) as the preferred solvent[3,4] activates anthraquinonyl ethers, giving higher yields and thereby permitting rearrangement at temperatures (50−105 °C) much lower than those required for thermal rearrangements.[7,8] However, some workers have found it necessary to reoxidize the primary products and have encountered the loss of a methoxy group para to a rearranging allyl group,[6] and in some cases the formation of anthracenone[9] or side chain double bond isomerization[10] has been reported. In our hands, problems with poor reproducibility have been experienced, and in this paper, we wish to introduce silver/potassium iodide (Ag/KI) in acetic acid as a new and efficient reagent for the reductive Claisen rearrangement of allyloxyanthraquinones.

Results and Discussion

We examined the title reaction for the use of Ag/KI and found that Ag/KI in AcOH is also able to promote Claisen rearrangement of allyloxyanthraquinones under mild conditions (110 °C). First, we examined the effect of Ag/KI on simple allyloxyanthraquinone under mild conditions. When allyl ether **1** was heated with Ag/KI (1:1 equiv) in AcOH at 110 °C, the Claisen rearrangement proceeded to furnish **8** in 97% yield after 30 min (Table 1).

As Table 1 also shows, the standard electrode potential for the half-reaction $AgX + e^- \rightleftharpoons Ag + X^-$ decreases with decreasing solubility product constant (K_{sp}) of AgX.[13] Therefore, the reducing ability of Ag/KX is favored as X^- changes from F^- to I^-, and an increase in the yield of the rearranged product is expected when Ag/KI is used as the reducing agent. It may be noted that only 0−10% of **8** is formed on prolonged heating of an *o*-xylene solution of **1** at 150 °C.[14] It is very likely that Ag/KI reduces the anthraquinone moiety to its electron-rich hydroquinone state, thereby facilitating the rearrangement in a manner a carbonium accelerates [3,3] sigmatropic rearrangement.[15−16] The extension of this new reagent to Claisen rearrangement of other allyloxyanthraquinones was also successful. Thus, Ag/KI rearranged the allyloxyanthraquinones to 2-allyl-1-hydroxyanthraquinones. Several examples of Claisen rearrangement of allyl ethers are shown in Table 2 and Scheme 1. As seen in Table 2 and Scheme 1, the reaction of allyloxyanthranquinones with Ag/KI affords 2-allyl-1-hydroxyanthraquinones in high yields.

Most notably, reductive Claisen rearrangements of 1,4-bisallyloxyanthraquinones can be carried out to give singly or doubly rearranged products with remarkable selectivity. Treatment of the bisallyloxyanthraquinone **2** under the above conditions gave only a low (17%) yield of **18**, the product of double Claisen rearrangement, together with mono Claisen rearrangement product **10**, whose yield depended on the time of the reaction.

However, when the reaction was carried out with Ag/KI (5 equiv each) for 90 min, the product of double rearrangement (**18**) was obtained in 68% yield. When this reaction was refluxed under air atmosphere for 16 h, the desired 2,3-diallylanthraquinone (**11**) was obtained in 65% yield.

In the case of the 1,8-diallyloxyanthraquinone **6**, the products and yields depended on the conditions used. The highest yield of double rearrangement products (**15**) was obtained when Ag/KI (2 equiv each) was used for 15 min. Of special note is that no demethoxylation and reduction of the carbonyl group occur with Ag/KI; for example, *p*-methoxy allyl ether **3** afforded the expected product **12** in 70% in 45 min.

Conclusions

In summary, Ag/KI is introduced as a new and efficient reagent in Claisen rearrangement of allyloxyanthraqui-

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Table 1. Claisen Rearrangement of 1-Allyloxyanthraquinone (1) to 2-Allyl-1-hydroxyanthraquinone (8) with Ag/KX in Refluxing Acetic Acid

entry	X	time (min)	yield (%)	K_{sp} of AgX	$E°$ [a]
1	F	240	5	b	
2	Cl	150	10	1.82×10^{-10}	+0.222
3	Br	45	95	5.2×10^{-13}	+0.073
4	I	30	97	8.3×10^{-17}	−0.151

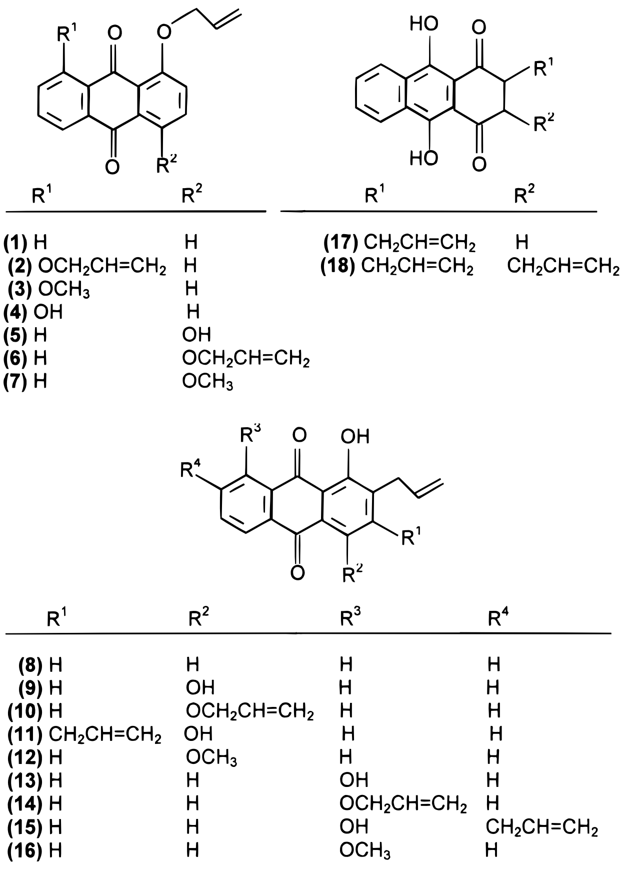
[a] Standard electrode potential for the half-reaction[11] $AgX + e^- \rightleftharpoons Ag + X^-$ (X: Cl, Br, I). [b] Solubility of AgF is 172 g/100 mL in water.[12]

Table 2. Reductive Claisen Rearrangement of Allyloxyanthraquinones

substrate	ratio[a]	time (min)	product	yield (%)
1	1:1:1	30	**8**	97
2	1:1:1	15	**10**	70
2	1:3:3	90	**18**	68
2	1:3:3[b]	960	**11**	65
3	1:1:1	45	**12**	70
4	1:5:5	45	**17**	65
4	1:5:5[b]	1020	**9**	60
5	1:1:1	40	**13**	90
6	1:1:1	20	**14**	60
6	1:2:2	15	**15**	95
7	1:1:1	45	**16**	97

[a] AQ:Ag:KI (equiv). [b] When the starting material was finished (90 and 45 min for compounds **2** and **3**, respectively), the reaction mixture was filtered, and the filtrate was heated at 85−90 °C until the final product was completed.

Scheme 1



	R1	R2
(1)	H	H
(2)	$OCH_2CH{=}CH_2$	H
(3)	OCH_3	H
(4)	OH	H
(5)	H	OH
(6)	H	$OCH_2CH{=}CH_2$
(7)	H	OCH_3

	R1	R2
(17)	$CH_2CH{=}CH_2$	H
(18)	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$

	R1	R2	R3	R4
(8)	H	H	H	H
(9)	H	OH	H	H
(10)	H	$OCH_2CH{=}CH_2$	H	H
(11)	$CH_2CH{=}CH_2$	OH	H	H
(12)	H	OCH_3	H	H
(13)	H	H	OH	H
(14)	H	H	$OCH_2CH{=}CH_2$	H
(15)	H	H	OH	$CH_2CH{=}CH_2$
(16)	H	H	OCH_3	H

nones. The present method has the following advantages: (a) the reagent is readily available and safe to handle, (b) the procedure is simple, (c) the reaction times are short that can be performed with a wide range of allyloxyanthraquinone derivatives, (d) work up is easy, and (e) demethoxylation, isomerization of double bonds, and reduction of carbonyl groups do not occur.

Experimental Section

Elemental analyses were performed at the National Oil Co. of Iran at Tehran Research Center.

General Procedure for Reductive Claisen Rearrangement of Allyloxyanthraquinones with Ag/KI. To a solution of allyloxyanthraquinone (1 mmol) in glacial acetic acid (15 mL) are added silver powder (1−5 mmol) and potassium iodide (1−5 mmol). The mixture is heated at reflux until TLC shows the reaction to be complete. Then, the reaction mixture is filtered, and water (60 mL) is added to the filtrate. The precipitate is removed by filtration and washed with water. If a precipitate does not form, the mixture is extracted with dichloromethane. The organic phase is washed with water, saturated $NaHCO_3$, and saturated NaCl and dried over sodium sulfate. After evaporation of solvent, a precipitate is obtained.

Data for compounds **8**, **10**, and **11** have been published previously in refs 16, 8, and 7, respectively.

1,4-Dihydroxy-2-(prop-2′-enyl)anthraquinone (9): red crystals (from acetone); mp 139−140 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.40−3.43 (d, 2H, $J = 7.5$ Hz), 5.09−5.15 (m, 2H), 5.84−6.01 (m, 1H), 7.08 (s, 1H), 7.71−7.75 (m, 2H), 8.22−8.26 (m, 2H), 12.83 (s, 1H), 13.27 (s, 1H) ppm; IR (KBr) 3670−3200 (b), 1630 (m) cm^{-1}; UV (MeOH) λ_{max} (log ϵ), 206.7 (4.18), 225.1 (4.05), 251.4 (4.28), 273.1(3.86), 482 (3.54) nm; MS *m/e* 280 (M, 100%), 262 ($M - H_2O$, 61%). Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.86; H, 4.28. Found: C, 72.65; H, 4.3%.

1-Hydroxy-4-methoxy-2-(prop-2′-enyl)anthraquinone (12): red solid; mp 118−119 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.50−3.53 (d, 2H, $J = 7.5$ Hz), 3.96 (s, 3H), 5.15−5.22 (m, 2H), 5.97−6.07(m, 1H), 7.21−7.24 (s, 1H), 7.70−7.77 (m, 2H), 8.23 (m, 2H), 13.38−13.41 (s, 1H) ppm; IR (KBr) 3640−3350 (b), 1660 (s), 1633 (m) cm^{-1} ; UV (MeOH) λ_{max} (log ϵ), 205.2 (4.44), 205.8 (4.42), 230.7 (4.48), 251.7 (4.64), 278.5 (4.14), 317.8 (3.54), 460 (4.20) nm; MS *m/e* 294 (M, 100%), 265 (M − CHO, 34.4%). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.47; H, 4.76. Found: C,73.1; H, 4.55%.

1,8-Dihydroxy-2-(prop-2′-enyl)anthraquinone (13): yellow needles (from ethanol); mp 131−132 °C; ^1H NMR ($CDCl_3$) δ 3.45 (d, 2H, $J = 6$ Hz), 4.8−6.4 (m, 3H),7.0−7.8 (m, 5H), 12.0 (s, 1H), 12.35 (s, 1H) ppm; IR (KBr) 3100−2800 (b), 1670 (s), 1620 (s),1600 (s) cm^{-1}; UV (MeOH) λ_{max} (log ϵ), 202 (4.36), 227 (4.63), 255 (4.38), 286 (3.99), 430.5 (4.05) nm; MS *m/e* 280 (M, 100%). Anal. Calcd for $C_{17}H_{12}O_4$: C, 72.86; H, 4.28. Found: C,73.0; H, 5.0%.

1-Hydroxy-2-(prop-2′-enyl)-8-(prop-2′-enyloxy)anthraquinone (14): yellow solid; mp 113−114 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.50−3.52 (d, 2H, $J = 5.0$ Hz), 4.77−4.78 (d, 2H, $J = 2.5$ Hz), 5.10−5.17 (m, 2H), 5.41 (dd, 1H), 5.70−5.71 (dd, 1H), 6.0 (m, 2H), 7.29−7.95 (m, 5H), 13.4 (s, 1H) ppm; IR (KBr) 3600−3100 (b), 3100−2800 (b), 1640 (s), 1610 (m) cm^{-1}; UV (MeOH) λ_{max} (log ϵ), 204.4 (4.314), 227 (4.98), 258.3 (4.311), 415 (3.84) nm; MS *m/e* 320 (M, 25.6%), 291 (M − CHO, 24.2%), 279 ($M - C_3H_5$, 70.6%). Anal. Calcd for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0. Found: C, 74.8; H, 4.75%.

1,8-Dihydroxy-2,7-bis(prop-2′-enyl)anthraquinone (15): yellow needles; mp 150−151 °C; ^1H NMR ($CDCl_3$) δ 3.35 (d, 4H, $J = 6$ Hz), 4.7−6.3 (m, 6H), 7.3 (d, 2H, $J = 8$ Hz), 7.55 (d, 2H, $J = 8$ Hz), 12.3 (s, 2H) ppm; IR (KBr) 3600−3300 (b), 3100−2900 (b), 1670 (s), 1640 (s) cm^{-1}; UV (MeOH) λ_{max} (log ϵ), 202 (3.97), 229 (4.25), 260 (4.07), 291 (3.58), 435 (3.69) nm; MS *m/e* 320 (M, 100%), 287 ($M - HO_2$, 13.2%), 265 ($M - C_3H_3O$, 13.4%). Anal. Calcd for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0. Found: C, 75.2; H, 5.1%.

1-Hydroxy-8-methoxy-2-(prop-2′-enyl)anthraquinone (16): yellow needles (from acetone); mp 158−159 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.54−3.57 (d, 2H, $J = 7.5$ Hz), 4.11 (s, 1H), 5.15−5.21 (m, 2H), 6.00−6.14 (m, 1H), 7.29−8.02 (m, 5H), 13.36 (s, 1H) ppm; IR (KBr) 3640−3200 (b), 3120−2800 (b), 1670 (m), 1640 (s) cm^{-1}; UV (MeOH) λ_{max} (log ϵ), 225 (4.72), 257.4 (4.48), 417.8 (3.95) nm; MS *m/e* 294 (M, 86.8%), 279 ($M - CH_3$, 100%). Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.47; H, 4.76. Found: C,73.2; H, 4.6%.

2-(Prop-2′-enyl)-9,10-dihydroxy-2,3-dihydro-1,4-anthracendione (17): yellow solid; mp 91−92 °C; ^{1}H NMR ($CDCl_3$) δ 2.33−2.63 (m, 2H), 2.80−3.05 (m, 3H), 5.03−5.1 (m, 2H), 5.67−5.74 (m, 1H), 7.64−7.70 (m, 2H) 8.31−8.34 (m, 2H), 13.42 (s, 1H), 13.48 (s, 1H) ppm; IR (KBr) 3100−2800 (b), 1635 (s) cm^{-1}; UV (MeOH) λ_{max} (log ϵ), 232.6 (4.217), 235.5 (4.216), 244.9 (4.19), 273.2 (4.00), 273.1 (4.01), 283.5 (4.03), 286.4 (4.05), 398.1 (4.08), 416.5 (4.06) nm; MS *m*/*e* 282 (M, 62.6%), 241 (M − C_3H_5, 100%). Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96. Found: C, 72.25; H, 4.75%.

2,3-Bis(prop-2′-enyl)-9,10-dihydroxy-2,3-dihydro-1,4-anthracendione (18): yellow solid; ^{1}H NMR ($CDCl_3$) δ 2.47−2.52 (m, 4H), 2.97−3.2 (m, 2H), 5.07−5.20 (m, 4H), 5.71−5.82 (m, 2H), 7.76−7.81 (m, 2H), 8.45−8.51 (m, 2H), 13.65 (s, 2H) ppm; IR (KBr) 3630−3300 (b), 3100−2800 (b), 1645 (s) cm^{-1}; UV (MeOH) λ_{max}, 203.4, 238.7, 258.6, 277.3, 399.2, 418.4. Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.53; H, 5.59. Found: C, 74.3; H, 5.35%.

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