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NOVEL SYNTHESIS OF TETRAHYDRO-2(1*H*)-QUINOLONES USING DIELS-ALDER REACTIONS OF 1-ARYLSULFONYL-2(1*H*)-PYRIDONES ACTING AS DIENOPHILES

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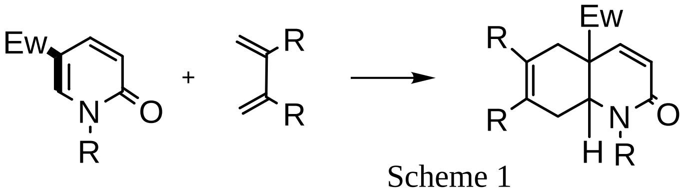
Abstract — 1-Arylsulfonyl-2(1*H*)-pyridones having an electron-withdrawing group at the 5-position were prepared, and the first example is presented relating to a novel synthetic methodology of tetrahydro-2(1*H*)-quinolones by Diels-Alder reactions of those with 2,3-dimethyl-1,3-butadiene.

2(1*H*)-Pyridones have aromaticity, nevertheless there are many publications relating to Diels-Alder (DA) reactions of 2(1*H*)-pyridones using as dienes.[1] However, little attention has been focused on the reactions of these compounds acting as dienophiles.[2] Previously, we have reported DA reactions of 2(1*H*)-pyridones having an electron-withdrawing group at the 4- or 6-position acting as dienophiles to give tetrahydro-1(2*H*)-isoquinolones.[2] To the best of our knowledge, there is no report for the syntheses of tetrahydro-2(1*H*)-quinolones using DA reactions of 2(1*H*)-pyridones acting as dienophiles. Considering the above reports, it is suggested that DA reactions of 2(1*H*)-pyridones bearing an electron-withdrawing group at the 5-position with dienes may give tetrahydro-2(1*H*)-quinolones as shown in Scheme 1. We tried DA reaction of 5- methoxycarbonyl-1-methyl-2(1*H*)-pyridone with 2,3-dimethyl-1,3-butadiene at 180 ℃ for 6 day in *o*-xylene, and unfortunately, the desired *cis*-4a,5,8,8a-tetrahydro-4a-methoxycarbonyl-1,6,7-trimethyl-2(1*H*)-quinolone (**A**) was obtained in a poor yield (3%) (Scheme 1). From this result, it is considered that 2(1*H*)-pyridones having two electron-withdrawing groups at the 1- and 5-positions have higher reactivity than 2(1*H*)-pyridones bearing that at the 5-position as dienophiles, since the electron-withdrawing group at the 1-position may decrease the delocalization of the unshared electrons on the nitrogen atom in the pyridone ring toward the dienophilic moiety, and that activates the dienophilic moiety. Herein,



Ew = electron-withdrawing group

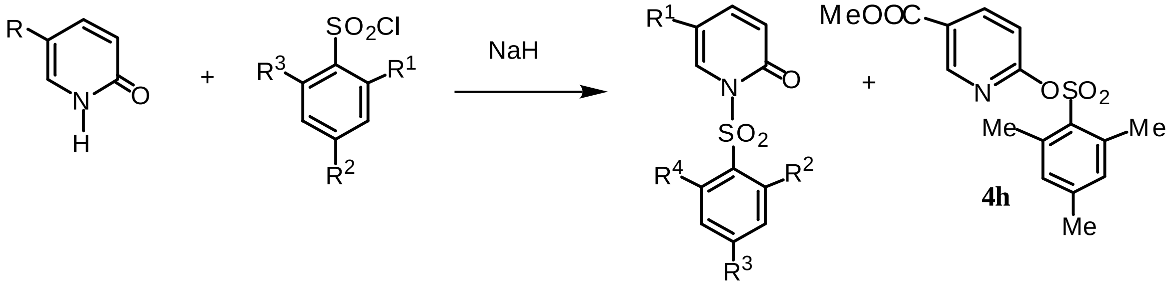
A : R = Me; Ew = COOMe

Scheme 1

the 1-position may decrease the delocalization of the unshared electrons on the nitrogen atom in the pyridone ring toward the dienophilic mmoiety, and that activates the dienophilic moiety. Herein, we wish to report the first example of a novel synthetic methodology of tetrahydro-2(1*H*)-quinolones by DA reactions of 1-arylsulfonyl-2(1*H*)-pyridones having an electron-withdrawing group at the 5-position with a diene.

Arylsulfonylations of 2(1*H*)-pyridones

The reactions of 2(1*H*)-pyridones (**1a-c**) with arylsulfonyl chlorides [**2a-f** (1.5 equiv.)] using NaH (1.5 equiv.) as a base in THF were carried out at 30 or 60 °C for 5 h, and the desired 1-arylsulfonyl-2(1*H*)-pyridones (**3a-h**) and 2-arylsulfonyloxypyridine (**4h**) were obtained, respectively, as shown in Table 1 and Scheme 2.



4h

1a : R = COOMe
1b : R = COMe
1c : R = NO_2

2a : R^2 = Me; R^1 = R^3 = H
2b : R^2 = OMe; R^1 = R^3 = H
2c : R^2 = Cl; R^1 = R^3 = H
2d : R^2 = NO_2; R^1 = R^3 = H
2e : R^1 = R^2 = R^3 = H
2f : R^1 = R^2 = R^3 = Me

3a : R^1 = COOMe; R^3 = Me; R^2 = R^4 = H
3b : R^1 = COMe; R^3 = Me; R^2 = R^4 = H
3c : R^1 = NO_2; R^3 = Me; R^2 = R^4 = H
3d : R^1 = COOMe; R^3 = OMe; R^2 = R^4 = H
3e
3f : R^1 = COOMe; R^3 = Cl; R^2 = R^4 = H
3g : R^1 = COOMe; R^3 = NO_2; R^2 = R^4 = H
3h : R^1 = COOMe; R^2 = R^3 = R^4 = H
: R^1 = COOMe; R^2 = R^3 = R^4 =Me

Scheme 2

Table 1. Reactions of **1a-c** with **2a-f** in the presence of NaH in THF

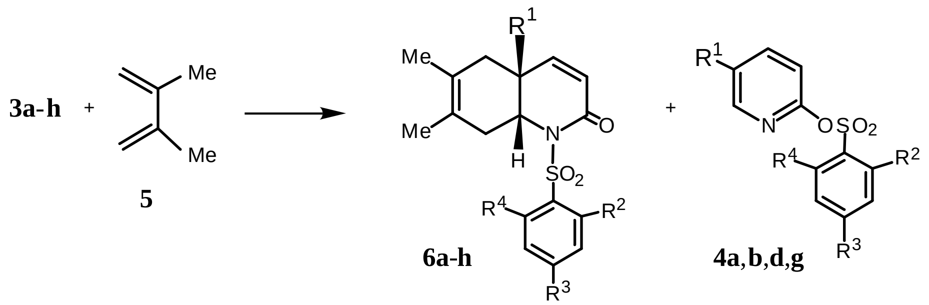
Entry	Compd **1**	Compd **2**	Temp. (℃)	Time (h)	Pyridone **3**	Yield (%)	Product **4**	Yield (%)
1	**a**	**a**	30	5	**a**	94		
2	**b**	**a**	60	5	**b**	60		
3	**c**	**a**	60	5	**c**	57		
4	**a**	**b**	60	5	**d**	91		
5	**a**	**c**	60	5	**e**	93		
6	**a**	**d**	60	5	**f**	43		
7	**a**	**e**	60	5	**g**	91		
8	**a**	**f**	30	5	**h**	33	**h**	33

As the results, the yields of **3a** (94%), **3b** (60%), and **3c** (57%) derived from the reactions of 5-methoxycarbonyl-, 5-acetyl-, and 5-nitro-2(1*H*)-pyridones (**1a-c**) with *p*-tosyl chloride (**2a**) decreased in order of the electron-attracting strength[3] (Entries 1-3). Next, the reactions of **1a** with 4-methoxybenzenesulfonyl, 4-chlorobenzenesulfonyl, and benzenesulfonyl chlorides (**2b**,**c**,**e**) gave **3d** (91%), **3e** (93%), and **3g** (91%) in high yields, respectively (Entries 4,5, and 7), but the same reactions of 4-nitrobenzenesulfonyl and 2,4,6-trimethylbenzenesulfonyl chlorides (**2d**,**f**) afforded **3f** (43%) and **3h** (33%) in moderate yields, besides **4h** as a mixture with **3h** (Entries 6 and 8).

DA reactions

DA reactions of **3a-h** with 2,3-dimethyl-1,3-butadiene [**5** (5 equiv.)] in *o*-xylene were performed at 120-180 ℃ for 2 day in a sealed tube and the desired tetrahydro-2(1*H*)-quinolones (**6a-h**) and **4a**,**b**,**d**,**g** were formed, respectively, as shown in Table 2 and Scheme 3. As the results, it was proved that there were little differences in the reactivity of **3a-c**, since DA reactions of **3a-c** with **5** gave **6a** (43%), **6b** (43%), and **6c** (39%) in the almost same yields, respectively (Entries 1-3). In addition, the reactions of **3g**,**h** with **5** gave satisfactory results [**6g** (67%) and **6h** (70%)] (Entries 7 and 8) and the same reactions of **3d-f** produced **6d** (52%), **6e** (43%), and **6f** (43%) in moderate yields, respectively (Entries 4-6). Furthermore, **4a**,**b**,**d**,**g** were formed as a mixture with **6a**,**b**,**d**,**g**, respectively (Entries 1,2,4, and 7). Considering the report[4] of Afarinkia *et al.*, **4a**,**b**,**d**,**g** would be produced by the intramolecular rearrangement of the arylsulfonyl group in **3a**,**b**,**d**,**g**, respectively. The stereochemistries of the ring juncture in **A** and **6a-h** were examined. The *cis*-stereochemistries of the ring juncture in **6a**,**b** were confirmed by the NOE measurement of ^{1}H-NMR spectra. Thus, when H-8a was irradiated in **6a**,**b**, the NOE was observed between H-8a and C$\underline{H}_3$OCO-4a (ca. 3.6%) in **6a**, and between H-8a and C$\underline{H}_3$CO-4a (ca. 6.4%) in **6b**. Furthermore, the *cis*-stereochemistries of the ring juncture in **A** and **6c-h** were deduced by comparing the ^{1}H-NMR spectral data of them with those of **6a**,**b**, respectively. The structures of all new compounds (**A**, **3a-h**, **4a**,**b**, **d**,**g**,**h**, and **6a-h**) were confirmed by IR, ^{1}H- and ^{13}C-NMR, and MS spectral analyses.

In conclusion, we have developed a novel synthetic methodology of tetrahydro-2(1*H*)-quinolones by using DA reactions of 2(1*H*)-pyridones acting as dienophiles. Further, applications and modifications of the methodology are in progress.



Scheme 3

Table 2. Diels-Alder reactions of **3a-h** with **5** in *o*-xylene

Entry	Pyridone **3**	Temp. (℃)	Time (d)	Adduct **6**	Yield (%)	Product **4**	Yield (%)
1	**a**	180	2	**a**	43	**a**	43
2	**b**	140	2	**b**	43	**b**	48
3	**c**	120	2	**c**	39		
4	**d**	180	2	**d**	52	**d**	35
5	**e**	140	2	**e**	43		
6	**f**	140	2	**f**	43		
7	**g**	180	2	**g**	67	**g**	31
8	**h**	160	2	**h**	70		

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