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A NEW SYNTHESIS OF DIHYDROPYRIDIN-2-ONES FROM BRASSARD'S DIENE AND IMINES

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Dedicated to Professor Dr. Ryoji Noyori on the occasion of his 70th birthday.

Abstract – A new method for the synthesis of dihydropyridin-2-ones from various *N*-2-nitrobenzenesulfonyl (nosyl) imines and 1,3-diethoxy-1-trimethylsiloxy-1,3-butadiene (Brassard's diene) under weakly-basic conditions is described. This synthesis of dihydropyridin-2-ones involves the initial addition reaction of Brassard's diene to imines to afford the adducts followed by a cyclization reaction that forms the corresponding 4-ethoxy-5,6-dihydro-*1H*-pyridin-2-ones in moderate to good yields after deprotection of its nosyl group from the adducts.

INTRODUCTION

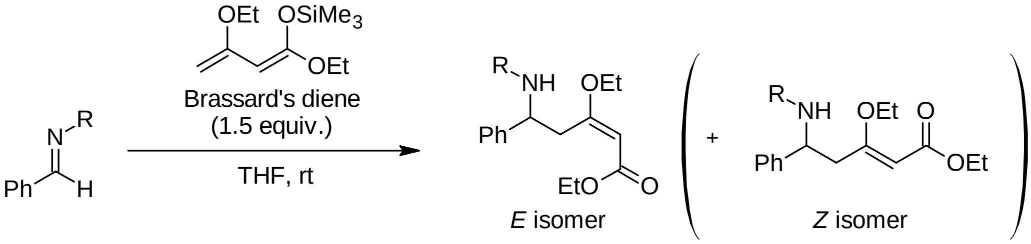
The derivatives of dihydropyridin-2-one that are often found in many biologically active compounds such as pharmaceuticals, agrochemicals and natural products are employed as useful building blocks of synthetic procedures of natural products. Aza Diels-Alder reactions between Brassard's diene and imines are considered to be the general method for the synthesis of the above compounds. This reaction is usually promoted by using stoichiometric amounts of Lewis acid such as boron trifluoride etherate, diethylaluminium chloride and ethylaluminium dichloride, and dihydropyridin-2-ones are afforded in good yields.[1] Recently, a reaction by using a catalytic amount of Brønsted acid was reported to promote the aza Diels-Alder reaction of Brassard's diene and imines.[2] However, those that use substrate having basic moieties such as amino or pyridyl groups were still considered difficult under these acidic conditions. Therefore, to develop a method which is applicable to the imine compounds was desired.

The imines having electron-withdrawing group on the nitrogen atom are well-known to be useful electrophiles in nucleophilic addition reactions. Also, it was reported from our laboratory that the addition reactions of organosilyl compounds such as Mannich-type reactions,[3] Strecker-type reactions,[4] trifluoromethylations[5] and cyanomethylations[6] proceeded under weakly Lewis basic conditions when *N*-sulfonyl imines[7] were used. Based on these results, a new synthesis of dihydropyridin-2-ones by using Brassard's diene and imines under neutral conditions was studied. Various dihydropyridin-2-ones were obtained under neutral conditions by the initial addition reaction of Brassard's diene to imines without using any additives, which was followed by cyclization under mild basic conditions.

RESULTS AND DISCUSSION

In the first place, reactions between Brassard's diene and various imines derived from benzaldehyde were tried at room temperature in THF, whose results are summarized in Table 1. When imines having an electron-withdrawing group such as *N*-tosyl (Ts) or *N*-nosyl (Ns) groups were used, addition reactions proceeded smoothly and the corresponding adducts were obtained in high yields with high (*E*) olefin selectivities (Entries 1 and 2). When *N*-*tert*-butoxycarbonyl (Boc) imine was used, the desired adduct was also obtained in moderate yield (Entry 3). As shown in entries 4 and 5, *N*-benzyl (Bn) and *N*-*p*-methoxyphenyl (PMP) imines did not give the corresponding products. Then, it was found that the reactions between *N*-sulfonyl imines and Brassard's diene without using Lewis acid or Lewis base proceeded smoothly and the expected adducts were obtained in high yields.

Table 1. Effects of substituents

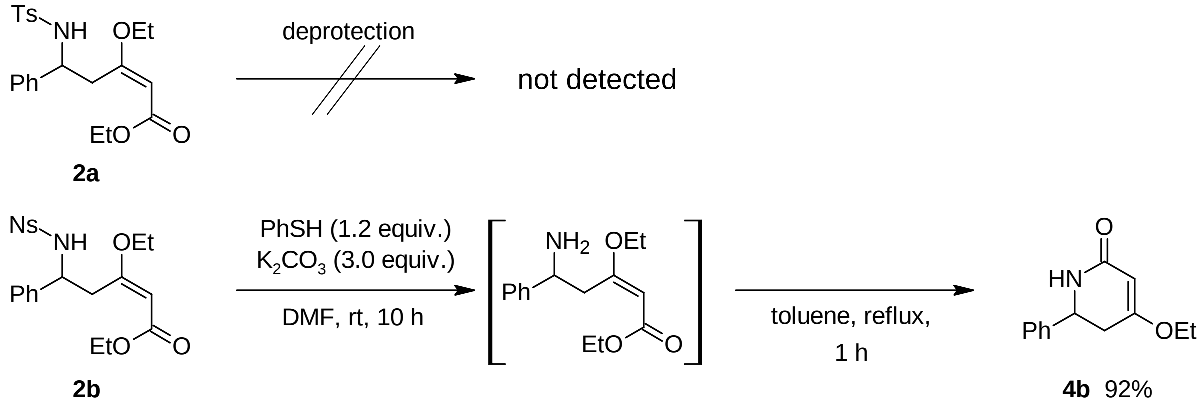


1a–**1e** **2a**–**2e** **3a**–**3e**

Entry	R	Time/h	Product	Yield[a]/%	*E*/*Z*
1	**1a**: Ts	1	**2a** & **3a**	98	>99:1
2[b]	**1b**: Ns	1	**2b** & **3b**	>99	95: 5
3	**1c**: Boc	10	**2c** & **3c**	72	82:18
4	**1d**: Bn	24	**2d** & **3d**	N.R.[c]	–
5	**1e**: PMP	24	**2e** & **3e**	N.R.[c]	–

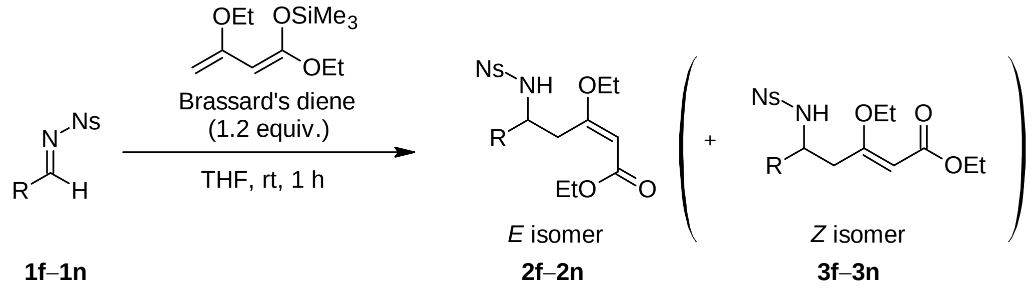
[a]Isolated yield. [b]1.2 equiv. of Brassard's diene was used. [c]No reaction.

Next, cyclizations of **2a** and **2b** were examined. Dihydropyridin-2-one was not obtained from **2a** because the deprotection of the tosyl group did not proceed under some conditions while **2b** gave the desired cyclic compound (**4b**) in 92% after the deprotection of the nosyl group according to the Fukuyama's procedure[8] (Scheme 1). Therefore, the nosyl group was chosen as a nitrogen protecting group.



Scheme 1. Deprotection and cyclization reactions of adduct **2a** and **2b**

Table 2. Addition reactions of Brassard's diene with various nosyl imines



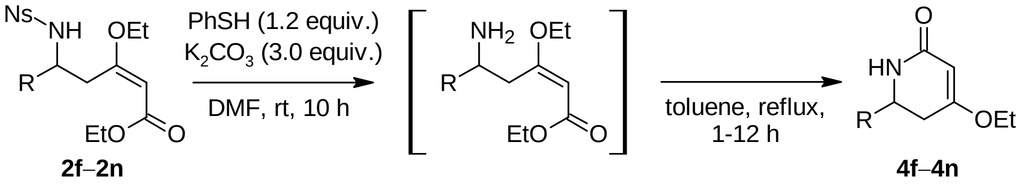
Entry	R	Product	Yield[a]/%	*E*/*Z*
1	**1f**: 4-MeC$_6$H$_4$	**2f** & **3f**	94	93:7
2	**1g**: 4-MeOC$_6$H$_4$	**2g** & **3g**	98	95:5
3	**1h**: 4-ClC$_6$H$_4$	**2h** & **3h**	92	95:5
4	**1i**: 4-O$_2$NC$_6$H$_4$	**2i** & **3i**	92	95:5
5	**1j**: 2-MeC$_6$H$_4$	**2j** & **3j**	96	94:6
6	**1k**: (*E*)-Ph-CH=CH	**2k** & **3k**	94	97:3
7	**1l**: 3-Pyridyl	**2l** & **3l**	97	97:3
8[b]	**1m**: 4-Me$_2$NC$_6$H$_4$	**2m** & **3m**	90	86:14
9	**1n**: *t*-Bu	**2n** & **3n**	74	95:5

[a]Isolated yield. [b]The reaction was carried out for 5 h.

The addition reactions of Brassard's diene with various *N*-nosyl imines were next tried (Table 2). *N*-Nosyl imines derived from aromatic aldehydes having electron-donating or -withdrawing groups reacted smoothly and afforded the corresponding adducts in high yields (Entries 1 - 4). Ortho-substituted imine also reacted smoothly to give the expected adduct in a high yield (Entry 5). In the case when α,β-unsaturated imine was used, the desired 1,2-addition product was obtained in a high yield (Entry 6). It is noteworthy that the imines having basic moieties such as pyridyl or dimethylamino groups were applicable in this reaction since these imines had not been used easily in the conventional Lewis acid- or Brønsted acid- mediated aza Diels-Alder reactions (Entries 7 and 8). Furthermore, an aliphatic imine prepared from pivalaldehyde gave the adduct in a moderate yield (Entry 9).

Next, cyclization reactions after the deprotection of the nosyl group of *E*-isomers were tried (Table 3). The deprotections were carried out with benzenethiol and potassium carbonate at room temperature in DMF, and then the cyclizations were conducted under refluxing in toluene to afford the corresponding dihydropyridin-2-ones. Both reactions of aromatic and aliphatic adducts gave the expected products in good to high yields, respectively. Adducts having a basic moiety such as pyridyl or dimethylamino groups also cyclized smoothly (Entries 7 and 8).

Table 3. Deprotection and cyclization reactions of *E*-isomers



Entry	R	Product	Yield[a]/%
1	**2f**: 4-MeC$_6$H$_4$	**4f**	92
2	**2g**: 4-MeOC$_6$H$_4$	**4g**	94
3	**2h**: 4-ClC$_6$H$_4$	**4h**	94
4	**2i**: 4-O$_2$NC$_6$H$_4$	**4i**	88
5	**2j**: 2-MeC$_6$H$_4$	**4j**	88
6	**2k**: (*E*)-Ph-CH=CH	**4k**	94
7	**2l**: 3-Pyridyl	**4l**	86
8	**2m**: 4-Me$_2$NC$_6$H$_4$	**4m**	82
9	**2n**: *t*-Bu	**4n**	92

[a] Isolated yield.

A new method for the preparation of 4-ethoxy-5,6-dihydro-*1H*-pyridin-2-ones was thus established by the reaction between Brassard's diene and *N*-nosyl imines. This synthetic procedure is applied conveniently to the substrates having basic moieties because the addition reactions with Brassard's diene proceeded under neutral conditions without using any additives and the following deprotection of the nosyl group proceeded under weakly-basic conditions.

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