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Efficient Synthesis of Tricyclic Benzobisoxazines by Silica Gel Catalysis

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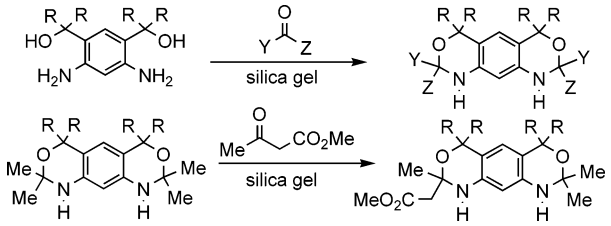

A new method for the synthesis of tricyclic benzobisoxazines, based upon silica gel-catalyzed formation of two 3,1-oxazine rings, is reported. The reversibility of the condensation reaction, forming an oxazine ring, allows for implementation of silica gel catalyzed ketone exchange in benzobisoxazine, thus enabling access to nonsymmetric derivatives of benzobisoxazines.

Benzoxazines, a well-known class of heterocyclic compounds, are of importance in the development of high-performance polymeric materials and in medicinal chemistry. Polybenzoxazines, which are conveniently obtained by ring-opening polymerization of 3,4-dihydro-2*H*-1,3-benzoxazine monomers, provide a new class of thermosetting resins for polymer composites with superior mechanical, flame-retardant, and superhydrophobic properties, especially for aerospace applications.[1] Derivatives of 3,4-dihydro-2*H*-1,3-benzoxazines and 2,3-dihydro-1,4-benzoxazines are well explored in medicinal chemistry,[2,3] with several drugs in clinical use. In contrast, 1,2-dihydro-4*H*-3,1-benzoxazines have received less attention, though derivatives with promising biological activity were recently discovered (Figure 1).[5−8] Recent syntheses and structure−activity relationship (SAR) studies of 6-aryl-1,2-dihydro-4*H*-3,1-benzoxazines and 6-aryl-1,2-dihydro-4*H*-3,1-benzoxazine-2-thiones led to the development of the potent and selective nonsteroidal progesterone receptor agonist Tanaproget (Figure 1).[5,6] In addition, acridines with 1,2-dihydro-4*H*-3,1-benzoxazine cores showed potent cytotoxic activities against selected human cancer lines.[7]

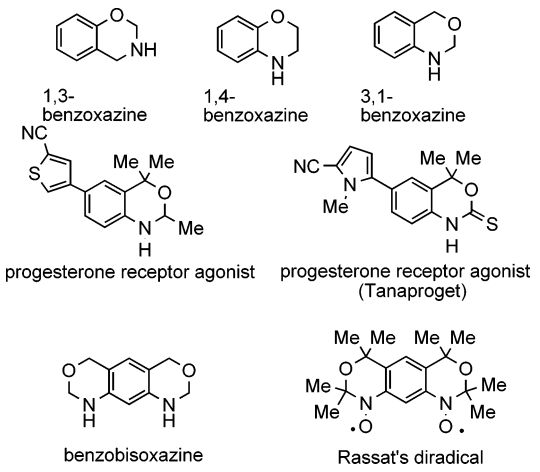

FIGURE 1. 1,3-, 1,4-, and 3,1-benzoxazine cores. Examples of 6-aryl-1,2-dihydro-4*H*-3,1-benzoxazines, 6-aryl-1,2-dihydro-4*H*-3,1-benzoxazine-2-thiones, benzobisoxazine core, and Rassat's diradical.

The most effective, and widely used, approaches to 1,2-dihydro-4*H*-3,1-benzoxazines are based upon the classical method of condensation, that is the acid-catalyzed condensation of *o*-aminobenzyl alcohols and aldehydes, or simple ketones.[9,10] The condensation conditions using acetic acid[11,12] or *p*-toluenesulfonic acid[5] in benzene or toluene provide moderate-to-good yields of the benzoxazines products. This method was applied by Rassat and co-workers to prepare the octamethyl derivative of benzobisoxazine, which was oxidized to form stable nitroxide diradical (Figure 1).[11] To our knowledge, this

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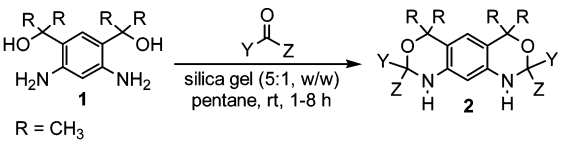
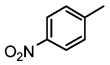
TABLE 1. Condensations of Diol−Diamine 1 with Aldehydes and Ketones[a]



entry	Y	Z	product	yield (%)
1	CH_3	H	**2a**	59
2		H	**2b**	33–46
3		H	**2c**	99
4			**2d**	75-78
5	CH_3	CH_3	**2e**	66-75
6	CH_2CH_3	CH_3	**2f**	44
7	$CH_2O(CH_2CH_2O)_3CH_3$	CH_3	**2g**	63–65
8	CH_2COOCH_3	CH_3	**2h**	30–37[b]

[a] The general procedure was used. All yields are isolated. [b] 0.05 M **1** and 50:1 w/w ratio of silica to **1** were used.

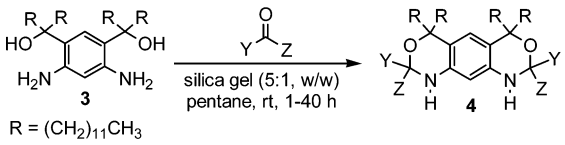
is the only report on benzobisoxazine with two saturated 3,1-oxazine rings annelated to a benzene ring.[13]

With our interest in high-spin organic molecules and polymers as building blocks for polymer magnets,[14] we have undertaken an investigation of the Rassat's nitroxide diradical and its derivatives. We optimized conditions for formation of octamethylbenzobisoxazine[11] in moderate yields, using the classical method of condensation.[15] In this process, we prepared the starting diol−diamines, e.g., **1** (R = CH_3) and **3** (R = $(CH_2)_{11}CH_3$). Compound **3** was purified by preparative TLC (PTLC), with a mixture of pentane and acetone used as eluent. To our surprise, only one dominant band was observed, which was determined to correspond to the desired tricyclic benzobisoxazine product **4b** (Table 2). We suspected that silica gel, which is a mild acid, acted as catalyst in the condensation reaction.

Silica gel, which is easily available, low cost, and nontoxic, has been used as a catalyst in organic synthesis.[16] The use of such a heterogeneous catalyst offers several advantages, such as the ease of crude product separation, potential catalyst reuse, and minimization of waste production. Therefore, we took further steps to explore an efficient, simple, and versatile method for synthesis of benzobisoxazines, using silica gel as catalyst.

We first investigated the silica gel catalyzed condensation

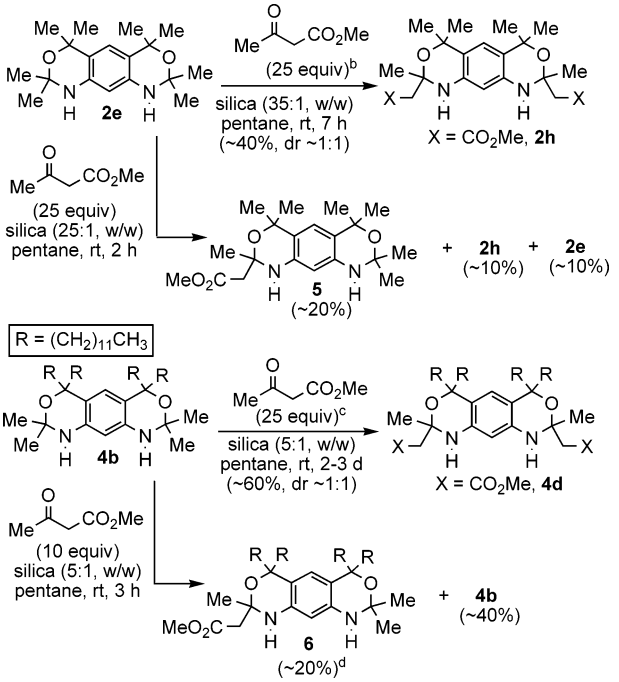
TABLE 2. Condensations of Diol-Diamine 3 with Aldehydes and Ketones[a]



entry	Y	Z	product	yield (%)
9	CH_3	H	**4a**	84
10	CH_3	CH_3	**4b**	66−76
11	$CH_2O(CH_2CH_2O)_3CH_3$	CH_3	**4c**	76
12	CH_2COOCH_3	CH_3	**4d**	66−85
13	CH_2COOCH_3	CH_2COOCH_3	**4e**	34−48

[a] The general procedure was used. All reported yields are isolated.

SCHEME 1[a]



[a] All reported yields are isolated. [b]Treatment with pentane allowed for partial separation of diastereomers. [c]Isolated with a 5−10% admixture of **6**. [d]Isolated as 5:1 mixture of **6** and **4d**.

of diol−diamine **1**[11,15] with aldehydes and ketones (Table 1).

The condensation reactions were carried out in pentane, at room temperature, in the presence of silica gel. When diol−diamine **1** was treated with aldehydes, the corresponding benzobisoxazine products were obtained cleanly and efficiently (entries 1−3, Table 1). 4-Nitrobenzaldehyde provided the benzobisoxazine product **2c** with 99% yield after purification (entry 3). Cyclohexanone and methyl alkyl ketones (entries 4−6) led to the expected products with good to moderate yields. Condensation of **1** with the PEGylated ketone, which is of interest for preparation of water-soluble high-spin diradicals,[17] gave **2g** with a good 65% isolated yield. Condensation of **1** with methyl acetoacetate progressed slowly and produced numerous side products; **2h** was isolated in a moderate 37%

(13) Two 3,1-oxazine rings could be annelated to acridine using relatively reactive formaldehyde ref 7.

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yield. For comparison, the acetic acid-catalyzed condensations provided **2d**, **2e**, and **2g** in 43−54%,[15] 20−34%,[15] and 22% yields, respectively, due to the formation of significant amounts of byproducts.

To further test the efficiency of this method, condensation of diamine−diol **3** with various carbonyl compounds were carried out (Table 2).

The condensation reactions were carried out as described for diol−diamine **1**. When diol−diamine **3** was treated with acetaldehyde, the reaction was completed after 1 h, to provide the bisannelation product **4a** in good yield. Condensations with methyl-substituted ketones (entries 10−12) also proceeded as expected. Although a large excess of ketone and long reaction times were required in the case of acetone, the resultant crude product **4b** already had adequate purity for synthetic purposes. For condensations with pegylated ketone as well as methyl acetoacetate, the target products were obtained in good to very good yields. It should be noted that benzobisoxazine **4c**, which contains both hydrophilic triethylene glycol groups and hydrophobic dodecane chains, is an amphiphilic heterocyclic molecule. From our perspective, **4c** is a precursor to a novel amphiphilic high-spin nitroxide diradical, with potential for biological and biomedical applications. Finally, we investigated the condensation with dimethyl 1,3-acetonedicarboxylate (entry 13). In this case, the condensation reaction progressed slowly (1−2 days) to give the bisannelation product in ∼30−50% yield after purification.

Benzobisoxazines **2h**, **4d**, and **4e** could have high synthetic value, as their ester groups can be readily reduced to the corresponding primary alcohols and then further functionalized.

It is expected that condensations of diol−diamines with ketones, leading to the benzobisoxazine products, are reversible. Therefore, we explored silica gel catalyzed exchange reaction to provide another approach to benzobisoxazines, including nonsymmetric benzobisoxazines with differently substituted oxazine rings, i.e., derived from two different ketones (Scheme 1).

Reaction of benzobisoxazines **2e** and **4b** with an excess amount of methyl acetoacetate gave benzobisoxazines **2h** and **4d** in ∼40% and ∼60% yields, respectively. This reaction corresponds to a complete exchange of acetone moiety for methyl acetoacetate moiety in both 3,1-oxazine rings.

When reactions of benzobisoxazines **2e** and **4b** with an excess amount of methyl acetoacetate were stopped at an intermediate stage, nonsymmetric benzobisoxazines **5** and **6** were obtained (Scheme 1). This result indicates a partial exchange of acetone moiety for methyl acetoacetate moiety. For the reaction of **2e** with methyl acetoacetate, benzobisoxazines **5**, **2h**, and unreacted **2e** were isolated in ∼20%, ∼10%, and ∼10% yields, respectively. However, reaction of **4b** with methyl acetoacetate gave **6** in ∼20% yield, with an admixture of **4d**, as chromatographic separation of the benzobisoxazine products was difficult, due to close R_f values.

Benzobisoxazines **2h** and **4d** were formed as ∼1:1 mixtures of diastereomers with indistinguishable R_f values on deactivated silica gel (Scheme 1). This is analogous to the benzobisoxazines that were obtained from condensations of diol−diamines (**1** and **3**) with aldehydes or unsymmetrically substituted ketones (entries 1−3, 6−9, 11, and 12).

Experimental Section

General Procedure for Condensation of Diol−Diamines 1 and 3 with Ketones and Aldehydes: Symmetric Benzobisoxazines 2a−h and 4a−e. Ketone or aldehyde (5−50 equiv) was added to a ∼0.1 M suspension of diol−diamine (5−500 mg) in pentane, followed by silica gel (5:1 w/w with respect to the diol−diamine). The reaction mixtures were vigorously stirred at room temperature. The disappearance of the starting material and the appearance of monoannelated, and then bisannelated products, were followed by TLC and, in selected cases, by ^{1}H NMR spectroscopy. After addition of ethyl acetate and filtration of silica, evaporation under reduced pressure gave the crude products, which were purified by PTLC or flash chromatography (silica, deactivated with 2% triethylamine in pentane). For benzobisoxazine **2e**, an alternative purification procedure involved treatment with pentane/ether (1:1). For benzobisoxazines **2g** and **4c**, the pegylated ketone, which was remaining in the crude reaction mixture, was washed off with water prior to chromatography.

General Procedure for Exchange Reaction of Benzobisoxazines 2e and 4b with Methyl Acetoacetate: Symmetric Benzobisoxazines 2h and 4d and Nonsymmetric Benzobisoxazines 5 and 6. Methyl acetoacetate (10−25 equiv) was added to a ∼0.05 M suspension of benzobisoxazine (5−60 mg) in pentane, followed by silica gel (5:1−35:1 w/w with respect to the benzobisoxazine). The reaction mixtures were vigorously stirred at room temperature. The disappearance of the starting material and the appearance of nonsymmetric, and then symmetric, benzobisoxazine products were followed by TLC and reactions leading to **5** or **6** by ^{1}H NMR spectroscopy. After addition of ethyl acetate and filtration of silica, evaporation under reduced pressure gave the crude products, which were purified by PTLC or flash chromatography (silica, deactivated with 2% triethylamine in pentane).

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Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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