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Chemical switching in reaction behavior of azine: Synthesis of a novel thienodiazepine derivative

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ABSTRACT

We previously have reported that an acid-promoted condensation of a hydrazonoester derived from phenylalanine afforded an azine which was converted to a pyrrole through 3 steps: isomerization to dienamine, [3,3]-sigmatropic rearrangement, and cyclization. In this study, reaction behavior of the intermediate proved to be switched depending on the type of the aromatic ring. Hydrazonoesters derived from thienylalanines afforded various thienodiazepine derivatives under thermal acidic conditions. A more reactive thiophene ring is likely to undergo Friedel-Crafts reaction prior to isomerization to dienamine.

Benzodiazepins play an important role in pharmacotherapy for anxiety and depressive psychosis (Fig. 1). Most of them have a bicyclic core consisting of benzene and 1,4-diazepine (i.e., 1,4-benzodiazepin), but 2,3-benzodiazepines including tofisopam are also used as anti-anxiety drugs. Furthermore, a bioisosteric replacement of benzene by thiophene created several anxiolytic thienodiazepines represented by etizolam.

Thiophene resembles benzene also in its chemical property. Although the degree is less than that of benzene, thiophene also has aromaticity. Therefore, not addition but substitution with various electrophiles takes place in the ring system. We previously reported a pyrrole synthesis by dimeric condensation of α-hydrazonoester, which was prepared by reduction of α-diazoester (Scheme 1) [1,2]. Thus, two molecules of α-hydrazonoester **1a** condense to form pyrrole diester **2a** along with removal of hydrazine and ammonia upon treatment with $SOCl_2$ in refluxing MeOH. In this reaction, the phenyl group at the β-position seems to be effective for obtaining satisfactory yield. We tried the dimeric condensation of α-hydrazonoester containing thiophene in expectation of its equivalency with benezene but met with unexpected chemical switching. This paper describes facile formation of thieno-2,3-diazepines by dimeric condensation of α-hydrazonoester with a thienyl group.

Hydrazonoesters **1b-c** were prepared from thienyl alanines **3b-c** (Scheme 2). Esterification of **3b-c** with $SOCl_2$ in MeOH generated **4b-c**, which were converted to α-diazoesters **5b-c** [3]. Reduction of **5b-c** with P(*n*-Bu)$_3$ gave (*E*)-hydrazonoesters **1b-c** as major products [4]. Furthermore, treatment of **1b** with $CaCl_2$ in toluene resulted in geometric isomerization to afford (*Z*)-hydrazonoester **1b'** [5]. Other hydrazonoesters **1d-1j** having electron-donating or electron-withdrawing substituents on thiophene rings were synthesized as follows. Upon treatment with LDA and DMF, **6d** and **6i** were formylated to give **7d** and **7i**, which were converted into esters **9d** and **9i** through Wittig reaction and subsequent hydrogenation with Pd/C. Esters **9d** and **9i** were transformed to **1d** and **1i** by the sequence of benzoylation, diazo transfer reaction [6] and reduction of the diazo group. In a similar manner, **1e-1h** were synthesized from commercially available aldehydes **7e-h**. However, hydrogenation of conjugated ester **8e-f** with bromothiophenes was carried out using Wilkinson's catalyst [7].

With various substrates containing a thienyl group in hand, dimeric condensation was examined. Treatment of **1b** with $SOCl_2$ in methanol under reflux did not give pyrrole **2b** but gave a non-pyrrole product for which the ^{1}H NMR spectrum showed geminally coupled methylene protons at δ 3.76 and 3.61 in $CDCl_3$ (Scheme 3). These signals suggested the presence of asymmetric center in the non-pyrrole product. Finally, the product was assigned to be 2,3-thienodiazepine **10b** by X-ray analysis (Fig. 2). Also, (*Z*)-isomer **1b'** generated **10b** in excellent yield.

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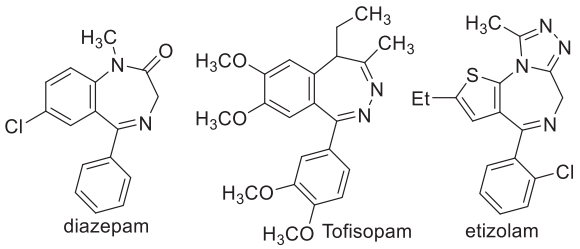
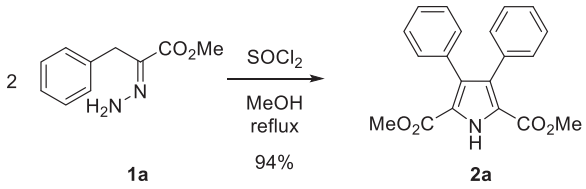
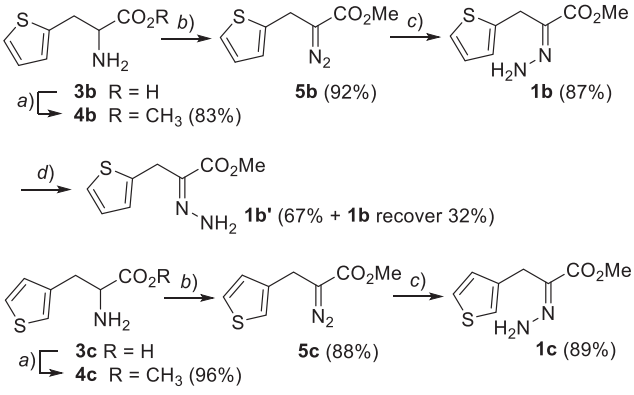
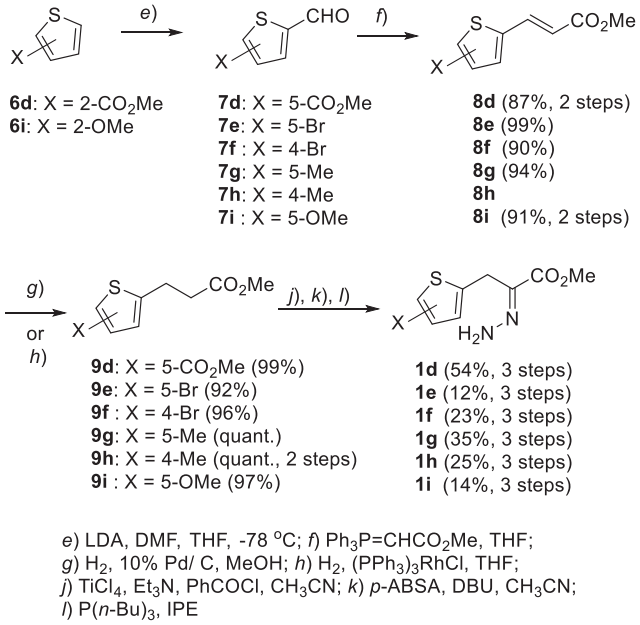


Fig. 1. Medicinal drugs containing a diazepine structure.

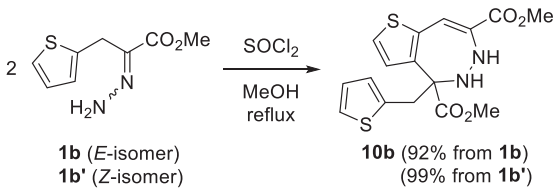


Scheme 1. Dimeric condensation of hydrazonoester of **1a**.





Scheme 2. Synthesis of hydrazonoesters.



Scheme 3. Dimeric condensation of hydrazonoester of **1b** and **1b′**.

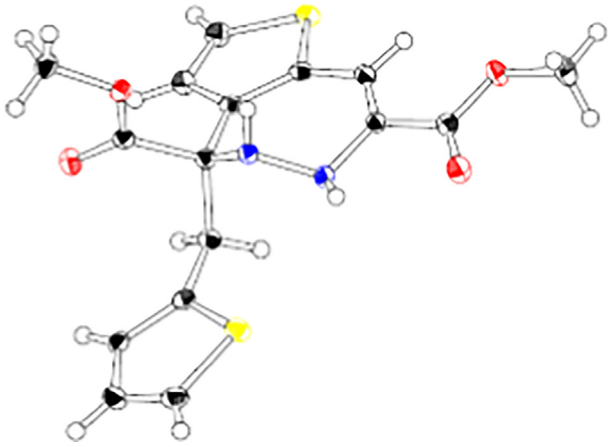
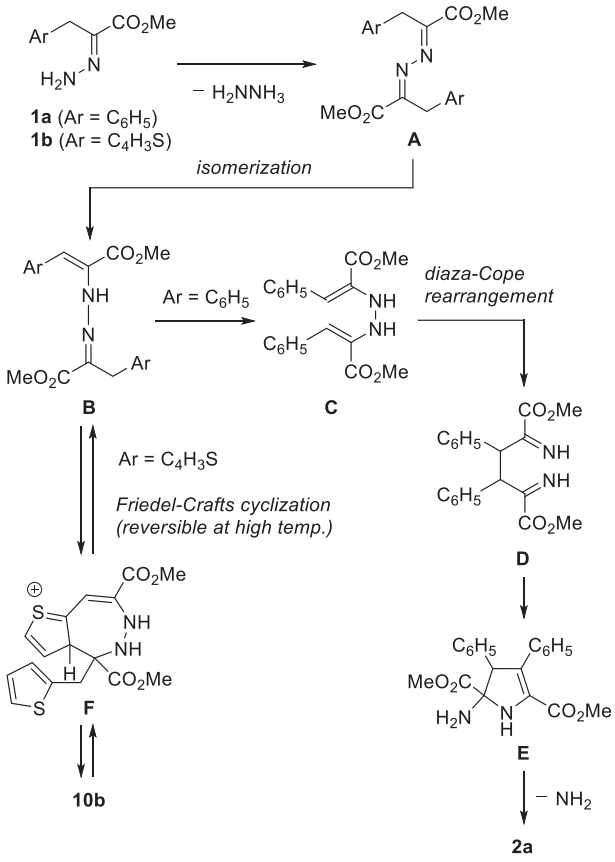


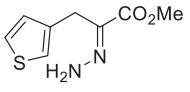
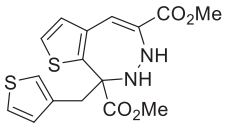
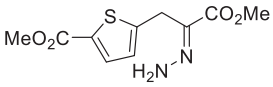
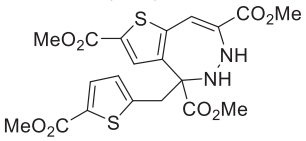
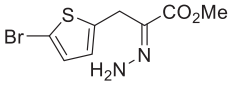
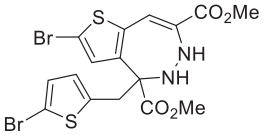
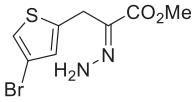
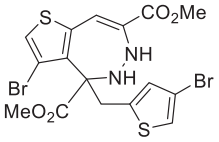
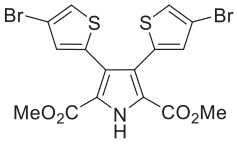
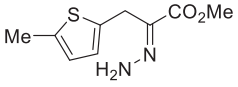
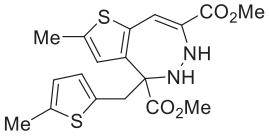
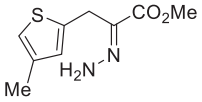
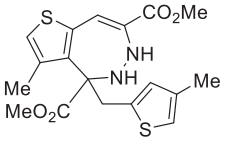
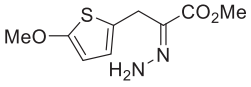
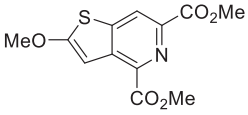
Fig. 2. X-ray analysis of **4e** (CCDC2056143)



Scheme 4. Chemical switching a dimeric condensation.

The chemical switching between thienodiazepine formation and pyrrole formation can be explained as follows (Scheme 4). The first step of both reactions is dimerization of hydrazonoester, giving enamine **B** with loss of hydrazine *via* azine **A** [8]. The next step diverges depending on the nucleophilic strength of aromatic rings in the intermediates. For the phenyl group, further double bond isomerization takes place to give dienamine **C**. Subsequently, diaza-Cope rearrangement of **C** results in the formation of diimine **D**, which is transformed to pyrrole **2a** by the sequence of cyclization and aromatization by removal of ammonia. On the other hand, for a more reactive thienyl group, Friedel-Crafts (F-C)-type reaction of **B** takes place prior to double bond isomerization to form 2,3-thienodiazepine **10b** through an intermediate **F**.

Table 1
Conversion of Hydrazonoesters.

Entry	Hydrazonester	Products
1	 **1c**	 **10c** (86%)
2	 **1d**	 **10d** (44%)
3	 **1e**	 **10e** (25%)
4	 **1f**	 **10f** (66%)
		 **2f** (34%)
5	 **1g**	 **10g** (85%)
6	 **1h**	 **10h** (59%)
7	 **1i**	 **11i** (30%)

1c-**1i** was refluxed in MeOH with $SOCl_2$.

Table 1 shows dimeric condensation of positional isomer **1c** on thiophene ring and derivatives **1d**-**1i** having electron-donating or electron-withdrawing substituents on the ring. Dimeric cyclization of **1c** occurred selectively at the 2′-position of thiophene to give thienodiazepine **10c** in 86% yield (Entry 1). Compound **1d** afforded thienodiazepine **10d** in 44% yield (entry 2). The ester group at the C5 position did not hinder F-C-type reaction at the C3 position. A bromide substituent at the C5 position lowered the reactivity of the F-C-type reaction and the yield of **10e** was only 25% (entry 3). On the other hand, the positional isomer **1f** yielded thienodiazepine **10f** (66%) and pyrrole **2f** (34%) (entry 4). Compound **1g** having a methyl group at the C5 position favored F-C-type reaction to give **10g** in excellent yield (entry 5). However, a methyl substituent at the C4 position lowered the yield of thienodiazepine **10h** (entry 6). A methoxy substituent directed an azine intermediate formed by condensation of **1i** toward another type of reaction to give thienopyridine **11i** (entry 7). The structure of **11i** was unequivocally determined by X-ray analysis (Fig. 3).

Scheme 5 shows plausible mechanistic pathway for the formation of **11i**. Due to the electron donation from oxygen of the methoxy group, intermediate **B** most likely undergoes *ipso*-cyclization to produce a spiro intermediate **G**. Then the methoxy thienomethyl group is removed [9] concomitant with formation of the cyclopropane ring to form **H**. Electron donation from sulfur leads to cleavage of cyclopropane ring, imine formation, and N—N bond cleavage. Subsequent cyclization proceeds along with removal of ammonia to form **11i**.

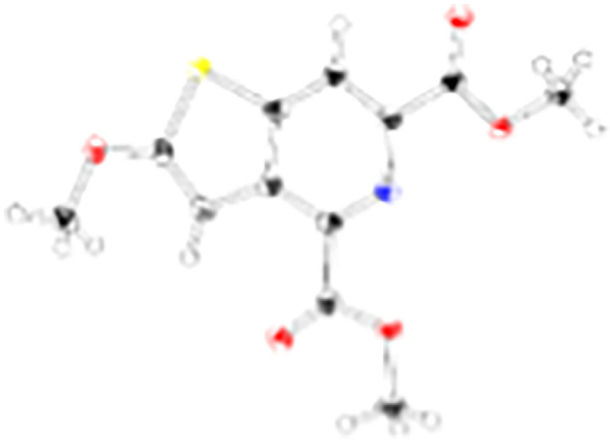
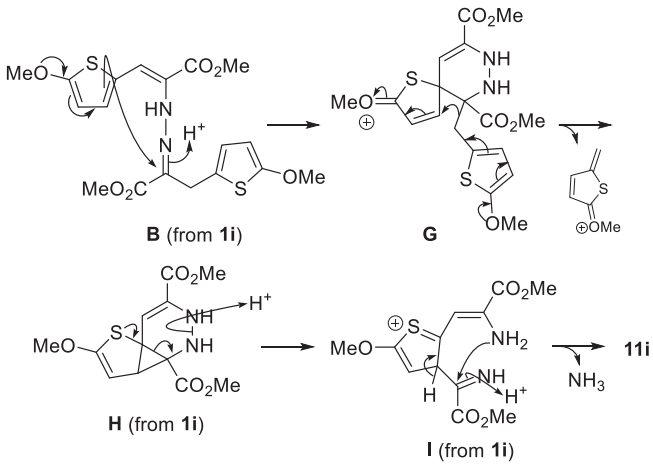


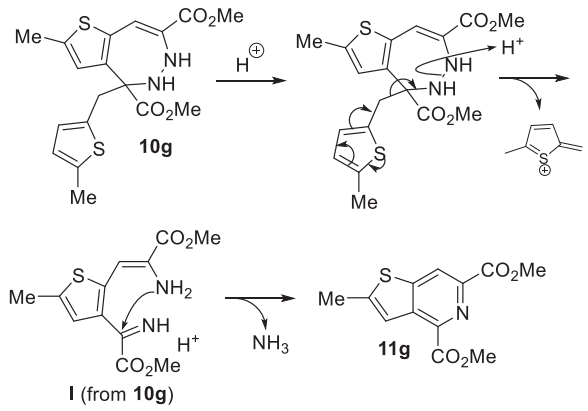
Fig. 3. X-ray analysis of **11i** (CCDC2055983)



Scheme 5. Plausible reaction mechanism for thienopyridine **11i**.

Table 2
Conversion of Thienodiazepine to Pyrrole.

Hydrazonoester	Product	Yield (%)
10b (R = H)	**2b** (R = H)	32
10d (R = CO_2Me)	**2d** (R = CO_2Me)	31
10g (R = Me)	**11g** (R = Me)	46



Scheme 6. Production of thienopyridine **11g**.

Finally, conversion of thienodiazepine to pyrrole was examined (Table 2). Heating of **10b** at 160 °C with 10-camphorsulfonic acid (CSA) in xylene in a sealed tube gave a pyrrole **2b** in 32% yield. Also, **10d** was converted into pyrrole **2d** in moderate yield upon treatment under the same conditions. The transformation commences with retro Friedel-Crafts reaction of protonated thiophene same as **F** that becomes possible at a higher temperature (Scheme 4). The resulting imine **B** should be converted into thermodynamically more stable **2b** in the same pathway as the reaction of **1a**. On the other hand, 5-Me thiophene **1g** gave a thienopyridine **11g** in 46%. Electrondonating effect of Me group caused elimination of methyl thienomethyl group [9] to yield intermediate **I** and subsequent cyclization gave **11g** (Scheme 6).

In conclusion, we have found that an azine produced from condensation of thienyl hydrazonoesters underwent a Friedel-Crafts-type reaction to yield a thienodiazepine derivative. Substituents on the thiophene ring changed the reactivity. Halogen substituents lowered the reactivity of Friedel-Crafts-type reaction of azine. Thienodiazepine derivatives were converted to pyrroles at a higher temperature through a retro Friedel-Crafts reaction. These newly synthesized compounds are expected to be good lead compounds for searching for bioactive substances.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153043.

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(b) N. Takamura, T. Mizoguchi, K. Koga, S. Yamada, Tetrahedron 31 (1975) 227–230.
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[8] Azine can't be isolated as the reaction proceed quickly to yield thienodiazepines.
[9] The thiophene derivative produced by elimination has not been isolated.