

# New Synthetic Equivalent of Nitromalonaldehyde Treatable in Organic Media

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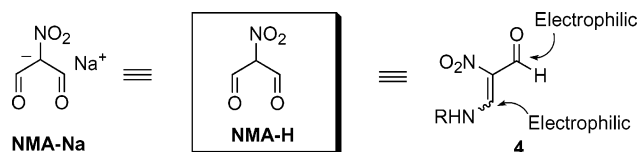
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$\beta$ -Nitroenamines having a formyl group at the  $\beta$ -position behave as the synthetic equivalent of unstable nitromalonaldehyde, which is a useful synthon for syntheses of versatile nitro compounds. High solubility of the nitroenamines into general organic solvents enables us to conduct reactions in the organic media accompanied by easy experimental manipulations and considerable safety. When nitroenamines are treated with 1,2-bifunctional nucleophiles such as hydrazines, hydroxylamine and glycine ester, nitrated pyrazoles, isoxazole and pyrrole-2-carboxylate were readily prepared. This methodology was also applicable to guanidines and 1,2-diamines, leading to pyrimidines and 1,4-diazepines, respectively.

## Introduction

Nitro compounds constitute an important class among organic compounds and are highly useful in synthetic chemistry.<sup>1–5</sup> Several preparative methods for nitro compounds have been developed. Nitration is the most powerful method for direct introduction of a nitro group into carbon skeletons although it often suffers from restrictions such as severe conditions, limited scope of substrates, and regioselectivity.<sup>1,2,6</sup> Oxidation of amines or oximes,<sup>1</sup> cycloaddition of nitroalkenes,<sup>1,7</sup> and Michael addition with nitroalkanes as nucleophiles<sup>1,8</sup> are also effective procedures; however, starting materials for these reactions are not always easily available. From this viewpoint, it is highly demanded to develop a compensatory method for the preparation of nitro compounds. As another methodology for construction of nitro compounds,



**FIGURE 1.** Synthetic equivalents of nitromalonaldehyde NMA-H.

a building block having a nitro group is built in the framework upon treatment with bifunctional nucleophiles. Nitromalonaldehyde (NMA-H) often appears as the synthon in retrosyntheses for various kinds of nitro compounds, but it actually cannot be employed because of instability. Its sodium salt (NMA-Na) has been used as the synthetic equivalent of NMA-H from previous times (Figure 1).<sup>9</sup> The salt NMA-Na is prepared from furfural via mucobromic acid with somewhat troublesome manipulations,<sup>10</sup> and the insolubility of NMA-Na into general organic solvents obliges us to conduct reactions in aqueous medium or in the highly polar solvent. Furthermore, crude NMA-Na is impact sensitive and thermally unstable, and it should be handled as a potentially explosive material.<sup>9</sup> Despite some serious problems mentioned here, NMA-Na is widely used even now for the synthesis of nitro compounds due to the absence of any other efficient reagents. Hence, it is highly desired to develop a convenient and safe synthetic equivalent of NMA-H treatable in organic media in place of NMA-Na.

In our course of study on ring-opening reactions of electron-deficient heterocyclic compounds, functionalized

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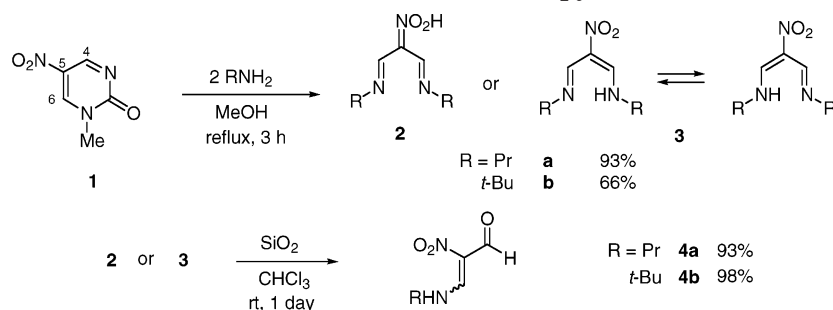
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SCHEME 1. Preparative Routes for Nitroenamines **4** from Nitropyrimidinone **1**

nitroenamines were found to be easily prepared.<sup>11,12</sup> Since the C4–C5–C6 moiety of 1-methyl-5-nitropyrimidin-2(1*H*)-one (**1**) could be regarded as the masked NMA-H, its aminolyzed products were considered to behave as the synthetic equivalent of NMA-H. When pyrimidinone **1** was heated with 2 equiv of primary amines in methanol, the ring-opening reaction readily proceeded to give oily product. In the <sup>1</sup>H NMR of the product, two substituents (R) on the nitrogens were equivalently observed, which indicated that the product was assigned as symmetrical diimine **2** or as a tautomeric mixture of azadienamines **3** under rapid equilibrium.<sup>12</sup> The X-ray crystallography and calculation of their heat of formation<sup>13a</sup> showed high possibility presenting in the latter structure **3**. When Schiff base **2** (or **3**) was charged on silica gel in a column and stood at room temperature for 1 day, the hydrolysis of an imino group proceeded to afford formylated nitroenamines **4** in good yields (Scheme 1).<sup>12</sup> This preparative method is advantageous from the viewpoint of easy modification of the substituent (R) on the amino group in **4**, namely the use of different amines in the initial aminolysis leads to nitroenamines having a modified amino group.

$\beta$ -Nitroenamines **4** possess two electrophilic sites, the  $\alpha$ -position and the formyl group, and this structural feature is considered to behave as the synthetic equivalent of NMA-H with easy manipulations and safety (Figure 1). In addition, high solubility into organic solvents will realize the use of **4** in organic media such as hexane, benzene, toluene, dichloromethane, chloroform, alcohols, and so on. In the present paper, we would like to show the synthetic utility of nitroenamines **4** affording nitrated azaheterocyclic compounds by condensation with bidentate nucleophiles.

## Results and Discussion

**A. Condensation with 1,2-Dinucleophilic Reagents.** The 4-nitropyrzole skeleton is focused on as the first target system, which is often found in the biologically active compounds or in their precursors.<sup>14–16</sup> To a solution of nitroenamine **4a** in methanol was added methylhydrazine **5a**, and the mixture was stirred at room

TABLE 1. Preparation of Nitropyrzoles **6**

Run	R	<b>6</b>	temp/°C	time/h	yield/%
1	Me	<b>a</b>	rt	3	96
2 <sup>a</sup>	H	<b>b</b>	rt	3	87
3 <sup>a</sup>	<i>t</i> -Bu	<b>c</b>	rt	24	29
4 <sup>a</sup>	<i>t</i> -Bu		80	3	59
5	CH <sub>2</sub> COOEt	<b>d</b>	rt	24	90
6 <sup>a</sup>	Ph	<b>e</b>	80	3	35
7	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	<b>f</b>	80	3	47
8 <sup>a</sup>	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>g</b>	80	3	0

<sup>a</sup> Equimolar amount of triethylamine was added.

temperature for 3 h. In the <sup>1</sup>H NMR of the residue after evaporation, signals for only 1-methyl-4-nitropyrzole **6a**<sup>16</sup> were observed, and further purification of **6a** was readily performed with column chromatography on silica gel. Nitroenamine **4a** reacted with other hydrazines **5b–f** to give corresponding pyrroles **6b–f**<sup>16</sup> (Table 1). The use of nitroenamine **4b** instead of **4a** did not cause a notable change in the yield of **6**. When reagents were commercially available as hydrazinium hydrochlorides, a equimolar amount of triethylamine was added to liberate hydrazine. In the case of sterically hindered hydrazine **5c**, the yield of **6c** was considerably lowered under ambient conditions, and it could be improved at elevated temperature. Ethyl hydrazinoacetate **5d** afforded difunctionalized pyrrole **6d** in good yield at room temperature. On the other hand, aromatic hydrazines **5e** and **5f** were less reactive even at 80 °C leading to pyrroles **6e** and **6f** in moderate yields, which was due to the low nucleophilicity of the nitrogen adjacent to the aromatic ring. Since hydrazines having a bulky alkyl or an aryl group are hardly soluble into water, it is difficult to conduct

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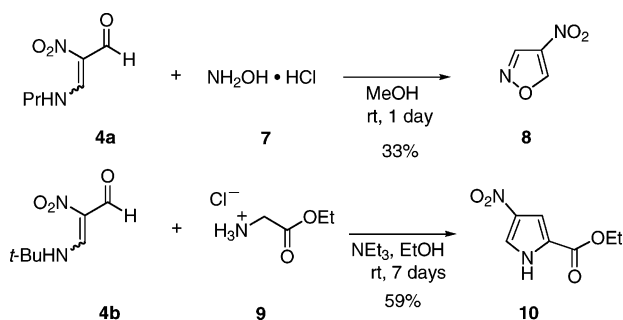
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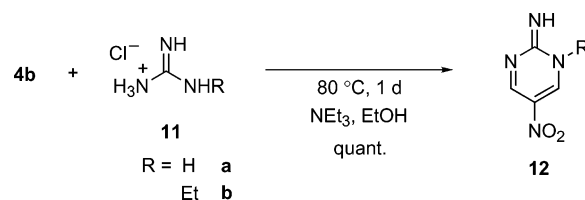
**SCHEME 2. Reactions of Nitroenamines 4 with Other 1,2-Dinucleophilic Reagents**


reactions with NMA-Na in the aqueous medium. Hence, the high solubility of **4** into organic solvents enables effective reactions in such cases.

Hydroxylamine hydrochloride **7** was employed as another 1,2-dinucleophilic reagent (Scheme 2). The condensation of nitroenamine **4a** with **7** occurred at room temperature, giving nitroisoxazole **8**<sup>15</sup> in a moderate yield; however, the reaction at higher temperature afforded only a complex mixture. Isolated nitroisoxazole **8** was transformed into unidentified products upon treatment with hydroxylamine hydrochloride at room temperature, thus the yield of **8** was lowered due to competitive decomposition of **8** under the same conditions. The synthetic utility of nitroenamine **4** can be shown since nitroisoxazole **8** has not been prepared from NMA-Na.<sup>9,15</sup>

Glycine ethyl ester hydrochloride **9** was usable as the nucleophile. Upon treatment of nitroenamine **4b** with **9** in the presence of triethylamine at 80 °C for 3 h, ethyl 4-nitropyrrole-2-carboxylate **10**<sup>17</sup> was isolated in 26% yield, and the yield of **10** was improved up to 59% when the reaction was conducted at room temperature for 7 days (Scheme 2). 4-Nitropyrrole-2-carboxylic acid derivatives and their reduced form, 4-amino derivatives, are useful building blocks for oligopyrrole peptides,<sup>18</sup> which bind in the minor groove of double-helical DNA. Recently it was energetically studied on versatile ligands for sequence-specific recognition in the DNA.<sup>19</sup> The presence of the carbonyl group at the 2-position is necessary for causing nitration at the 4-position, but introduction of the carbonyl group into the pyrrole ring often accompanies multistep reactions and troublesome manipulations.<sup>20</sup> Although another approach to **10** with NMA-Na is also known,<sup>17</sup> this method suffers from restrictions mentioned at the beginning of this paper. Hence, our preparative method for pyrrole **10** is concluded to be superior to other methods.

**B. Condensation with 1,3-Dinucleophilic Reagents.** 2-Amino-5-nitropyrimidine was focused on as the target skeleton having a six-membered ring. When nitroenamine **4b** and guanidine hydrochloride **11a** were

**SCHEME 3. Synthesis of Nitropyrimidine Derivatives 12**


heated with potassium *tert*-butoxide at 80 °C for 1 day, only a complex mixture was obtained, and we obtained no evidence for formation of pyrimidine derivative **12a**. The desired condensation proceeded to give **12a**<sup>21</sup> in a quantitative yield in the reaction with triethylamine instead of *tert*-butoxide (Scheme 3). *N*-Ethylguanidine **11b** similarly reacted under the same conditions affording pyrimidine **12b**. It was determined that the ethyl group was attached to the ring nitrogen since two different aromatic protons were observed in the <sup>1</sup>H NMR. Nitroenamine **4** was also proved to react with 1,3-dinucleophilic reagents easily, which resulted in the construction of a six-membered ring.

**C. Condensation with 1,4-Dinucleophilic Reagents.** The diazepine skeleton is also important for drug design, and numerous diazepines have been prepared up until now.<sup>22</sup> However, 6-nitro[1,4]diazepines are rarely seen in the literature except for a few papers dealing with 5,7-diphenyl and 5,7-dimethyl derivatives<sup>23</sup> and the 2,2-dimethyl derivative.<sup>24</sup> From this viewpoint, we studied the reaction of nitroenamine **4b** with 1,2-diamines leading to 2,3-disubstituted 6-nitrodiazepines **14**.

When 1,2-diaminoethane **13a** was added to a methanol solution of nitroenamine **4b**, white precipitates were immediately generated. After the mixture was stirred at room temperature for 3 h, white precipitates were filtered off (product **15a**, yield 31%, based on **4b**), and then the filtrate was concentrated to afford white solid (diazepine **14a**, yield 69%). Both products gave the same empirical formulas with elemental analyses. While the low solubility of **15a** into organic solvents prevented the recrystallization and the structural determination, it was considered to be a mixture of oligomers in which the dimer (*n* = 1) was probably the major product. Quantitative synthesis of diazepine **14a** was realized by slowly adding a solution of diamine to a solution of nitroenamine **4b** to avoid oligomerization (Table 2).

The present reaction was applicable to alkyl-substituted diamines **13b,c** to give corresponding diazepines **14b,c** in good yields. Both isomeric 1,2-diaminocyclohexanes **13d,e** effectively furnished bicyclic diazepines **14d,e** fused in the *cis* and *trans* mode, respectively. In the case of 1,2-diaminobenzene **13f**, different reactivity from other 1,2-diamines was revealed. In the mass spectrum of red solid precipitated during the reaction, a parent peak for dimeric structure **15f** was observed; however, the peak for benzodiazepine **14f** was not detected. Although larger

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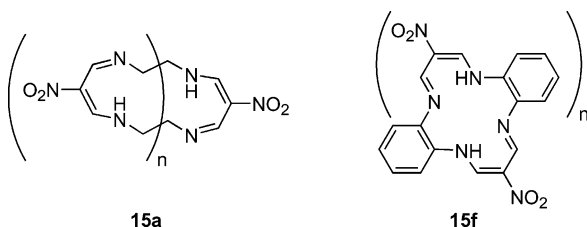
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TABLE 2. Preparation of Nitrodiazepines 14

run	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	14	yield/%
1	H	H	H	<b>a</b>	quant.
2	Et	H	H	<b>b</b>	80
3	H	Me	H	<b>c</b>	69
4	H	–(CH <sub>2</sub> ) <sub>4</sub> – (cis)	H	<b>d</b>	79
5	H	–(CH <sub>2</sub> ) <sub>4</sub> – (trans)	H	<b>e</b>	86
6	H	<i>o</i> -phenylene group	H	<b>f</b>	0

oligomer might be formed as a byproduct, the major content was considered to be dimer **15f** ( $n = 1$ ), and we have obtained no evidence for the presence of diazepine **14f**<sup>25</sup> in the mixture. In this case, dilution of the reaction mixture was not effective and **15f** was also afforded. The lack of flexibility of diaminobenzene **13f** was considered to be a reason for this different reactivity. In consideration of the recent spotlight on the  $\beta$ -diketiminato ligand,<sup>13</sup> oligomers **15** might also be useful as multidentate ligands having nitro groups.

FIGURE 2. Oligomeric structures derived from **4b** and **13**.

## Summary

Nitroenamines **4** are revealed to behave as the synthetic equivalent of NMA-H constructing five-, six-, and seven-membered rings upon treatment with bifunctional nucleophiles, and leading to nitrated azaheterocycles. While the conventional synthetic equivalent NMA-Na has serious problems for employment in organic syntheses, the present nitroenamines **4** solve these problems, especially safety issues. High solubility of **4** into general organic solvents simplifies experimental manipulations, and enables the use of bifunctional nucleophiles that are not treatable in organic media. Hence, synthesis of hitherto unknown nitro compounds becomes possible by use of nitroenamine **4**. The synthetic utility of nitroenamine **4** is concluded to be higher than that of NMA-Na from the viewpoint of both treatability and safety.

## Experimental Section

**Preparation of Nitroenamine 4a.**<sup>12</sup> Nitropyrimidinone **1** was prepared in 70% overall yield by the condensation of commercially available 1,1,3,3-tetramethoxypropane and *N*-methylurea in 12 M hydrochloric acid<sup>26</sup> followed by nitration

with nitric acid in sulfuric acid. To a solution of pyrimidinone **1** (310 mg, 2 mmol) in methanol (40 mL) was added propylamine (410  $\mu$ L, 5 mmol), and the mixture was heated under reflux for 3 h. After evaporation, the residue was extracted with hexane ( $3 \times 30$  mL), and removal of hexane afforded NMR pure diimine **2a** (or azadienamine **3a**) (390 mg, 1.96 mmol, 98%) as pale yellow oil. A solution of **2a** (or **3a**) (200 mg, 1 mmol) in chloroform (5 mL) was charged on silica gel (20 g) in a column and stood at room temperature for 1 day, and then it was eluted with chloroform. The solvent was removed under reduced pressure to give nitroenamine **4a** (150 mg, 93%). Nitroenamine **4b**<sup>12</sup> was similarly prepared by use of *tert*-butylamine instead of propylamine.

**1-*tert*-Butyl-4-nitropyrazole (6c).** To a solution of nitroenamine **4a** (244 mg, 1.54 mmol) in methanol (10 mL) were added *tert*-butylhydrazine hydrochloride (212 mg, 1.70 mmol) and triethylamine (0.23 mL, 1.70 mmol). The resultant solution was heated under reflux for 3 h, and concentrated under reduced pressure. The residue was treated with column chromatography on silica gel to give **6c** (eluted with benzene/chloroform = 1/1, 153 mg, 0.90 mmol, 59%) as yellow needles. Mp 76–77 °C. IR (KBr/cm<sup>–1</sup>) 1502, 1311; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.62 (s, 9H), 8.09 (s, 1H), 8.25 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  29.3 (q), 60.7 (s), 125.5 (d), 134.3 (s), 135.3 (s). Anal. Calcd for C<sub>7</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: C, 49.69; H, 6.55; N, 24.83. Found: C, 49.80; H, 6.73; N, 24.58. When other hydrazines were employed, experiments were carried out in a similar way. Pyrazoles **6a–f** except for **6c** could be found in the literature.<sup>16</sup>

**4-Nitroisoxazole (8).**<sup>15</sup> To a solution of nitroenamine **4a** (296 mg, 1.87 mmol) in methanol (10 mL) was added hydroxylamine hydrochloride **7** (143 mg, 2.06 mmol), and the resultant solution was stirred at room temperature for 1 day. After concentration, the residue was extracted with diethyl ether ( $3 \times 20$  mL), and removal of the solvent afforded yellow oil. Upon treatment with column chromatography on silica gel, isoxazole **8** (eluted with benzene, 69 mg, 0.61 mmol, 33%) was isolated as yellow needles.

**Ethyl 4-Nitropyrrole-2-carboxylate (10).**<sup>17</sup> To a solution of nitroenamine **4b** (346 mg, 2.0 mmol) in ethanol (30 mL) were added glycine ethyl ester hydrochloride **9** (562 mg, 4.0 mmol) and triethylamine (0.84 mL, 6.0 mmol), and the mixture was stirred at room temperature for 7 days. After removal of ethanol, chloroform (30 mL) was added, and precipitated *tert*-butylammonium chloride was filtered off. The filtrate was concentrated, and the residue was treated with column chromatography on silica gel to afford pyrrole **10** (eluted with chloroform, 218 mg, 1.19 mmol, 59%) as a yellow powder.

**3-Ethyl-2-imino-5-nitropyrimidine (12b).** To a solution of nitroenamine **4b** (172 mg, 1.0 mmol) in ethanol (30 mL) were added *N*-ethylguanidine hydrochloride **11b** (247 mg, 2.0 mmol) and triethylamine (0.28 mL, 2.0 mmol), and the mixture was heated at 80 °C for 1 day. After removal of ethanol, the residue was extracted with chloroform ( $3 \times 30$  mL). The organic layer was dried over magnesium sulfate and concentrated to give almost pure pyrimidine **12b** (336 mg, 2.0 mmol, quant.). Further purification was performed by recrystallization from benzene giving **12b** as colorless plates. Mp 140–146 °C dec. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.30 (dd,  $J = 7.3, 7.3$  Hz, 3H), 3.58 (q,  $J = 7.3$  Hz, 1H), 3.59 (q,  $J = 7.3$  Hz, 1H), 6.0–6.2 (br, 1H), 9.03 (d,  $J = 3.2$  Hz, 1H), 9.12 (d,  $J = 3.2$  Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  14.1 (q), 36.0 (t), 133.4 (s), 153.9 (d), 154.4 (d), 162.5 (s); MS (FAB) 169 ( $M^+ + 1$ , 100%). Anal. Calcd for C<sub>6</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>: C, 42.86; H, 4.80; N, 33.32. Found: C, 43.23; H, 4.92; N, 33.52.

**The Typical Procedure for Synthesis of Diazepines 14.** To a solution of nitroenamine **4b** (258 mg, 1.50 mmol) in methanol (30 mL) was added a solution of 1,2-diaminoethane **13a** (0.10 mL, 1.50 mmol) in methanol (10 mL). The resultant solution was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was washed with

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a small amount of benzene to afford diazepine **14a** (211 mg, 1.49 mmol, quant.) as a pale yellow powder.

**2,3-Dihydro-6-nitro-1H-1,4-diazepine (14a).** Mp 194–195 °C dec. IR (KBr/cm<sup>-1</sup>) 1571, 1344; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 3.65 (s, 4H), 8.50 (s, 2H), 9.3–9.6 (br, 1H); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ 50.8 (t), 122.0 (s), 151.2 (d); MS (FAB) 142 (M<sup>+</sup> + 1, 100%). Anal. Calcd for C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.80; H, 5.05; N, 29.67. When other diamines **13** were employed, experiments were carried out in a similar way.

**2,3-Dihydro-1-ethyl-2-methyl-6-nitro-1H-1,4-diazepine (14b).** Yellow powder; mp 84–85 °C. IR (KBr/cm<sup>-1</sup>) 1589, 1377; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.38 (t, *J* = 7.2 Hz, 3H), 3.2–3.8 (br, 2H), 3.58 (q, *J* = 7.2 Hz, 2H), 3.8–4.1 (br, 2H), 8.51 (s, 1H), 8.73 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 14.0 (q), 53.5 (t), 54.0 (t), 56.0 (t), 123.3 (s), 149.0 (d), 155.3 (d); MS (FAB) 170 (M<sup>+</sup> + 1, 100%). Anal. Calcd for C<sub>7</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.86; H, 6.59; N, 24.51.

**2,3-Dihydro-2-methyl-6-nitro-1H-1,4-diazepine (14c).** Pale yellow powder; mp 170–171 °C. IR (KBr/cm<sup>-1</sup>) 1567, 1295; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.20 (d, *J* = 3.8 Hz, 3H), 3.2–3.4 (br, 1H), 3.62 (d, *J* = 4.4 Hz, 2H), 8.41 (s, 1H), 8.51 (s,

1H), 8.5–9.3 (br, 1H); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>) δ 20.0 (q), 57.1 (t), 57.4 (d), 123.7 (s), 149.7 (d), 152.6 (d); MS (FAB) 156 (M<sup>+</sup> + 1, 100%). Anal. Calcd for C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.29; H, 5.90; N, 26.75.

**cis-5a,6,7,8,9a-Hexahydro-3-nitro-1H-benzo[*b*][1,4]-diazepine (14d).** White powder; mp 260–261 °C. IR (KBr/cm<sup>-1</sup>) 1573, 1336; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.1–1.3 (br, 1H), 1.4–1.8 (br, 6H), 2.0–2.1 (br, 1H), 3.5–3.7 (br, 1H), 3.8–4.0 (br, 1H), 8.27 (s, 1H), 8.49 (br s, 2H); <sup>13</sup>C NMR could not be measured because of low concentration of the sample; MS (FAB) 196 (M<sup>+</sup> + 1, 100%). Anal. Calcd for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.04; H, 6.71; N, 21.86.

**trans-5a,6,7,8,9a-Hexahydro-3-nitro-1H-benzo[*b*][1,4]-diazepine (14e).** White powder; mp 216–217 °C. IR (KBr/cm<sup>-1</sup>) 1573, 1311; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 1.1–1.3 (br, 2H), 1.3–1.5 (br, 2H), 1.6–1.8 (br, 2H), 2.2–2.3 (br, 2H), 2.9–3.1 (br, 2H), 8.30 (s, 1H), 8.37 (br s, 2H); <sup>13</sup>C (100 MHz, DMSO-*d*<sub>6</sub>) δ 23.4 (t), 33.7 (t), 61.5 (d), 121.1 (s), 149.1 (d); MS (FAB) 196 (M<sup>+</sup> + 1, 100%). Anal. Calcd for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.30; H, 6.63; N, 21.82.

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