Tetrahedron 67 (2011) 6347–6351

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Divergent synthesis of fully substituted isoxazoles and spiro-fused pyrazolin-5-ones from cyclopropyl oximes

Xiaolan Fu [a], Peng Huang [b], Guangyuan Zhou [b,*], Yinqiao Hu [a], Dewen Dong [a,b,*]

[a] Department of Chemistry, Northeast Normal University, Changchun 130024, PR China
[b] Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, 5625 Renmin Street, Changchun 130022, PR China

ARTICLE INFO

Article history:
Received 10 April 2011
Received in revised form 24 May 2011
Accepted 31 May 2011
Available online 14 June 2011

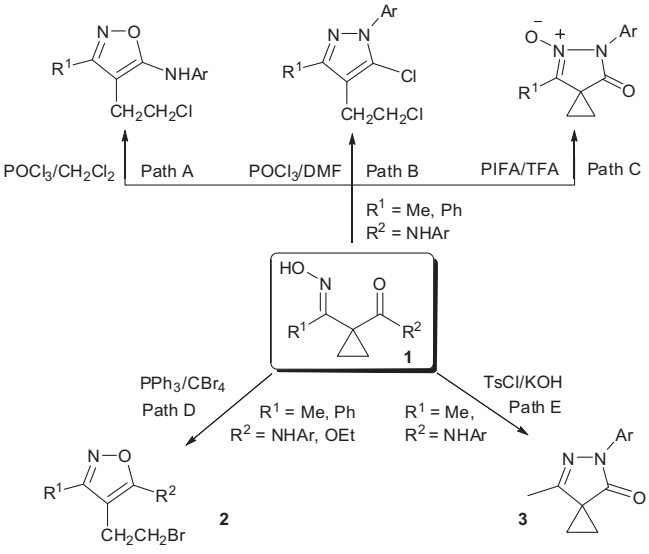
ABSTRACT

Efficient and divergent synthesis of fully substituted isoxazoles and spiro-fused pyrazolin-5-ones is developed from cyclopropyl oximes based on selection of reaction conditions. Under Appel conditions (PPh_3/CBr_4), substituted isoxazoles were synthesized from cyclopropyl oximes via a ring-opening and intramolecular cyclization process, whereas by treatment of cyclopropyl oximes with *p*-toluenesulfonyl chloride in the presence of potassium hydroxide, spiro-fused pyrazolin-5-ones were obtained via tandem ketoxime tosylation and intramolecular cyclization.

1. Introduction

Five-membered nitrogen-containing heterocycles have received intensive research interests due to their biological activities, and found a wide range of applications in pharmaceutical and agrochemistry.[1] Among them, the isoxazole and pyrazolin-5-one motifs make up the core structures of numerous natural products and biologically active synthetic compounds.[2,3] General methods for their synthesis involve the intermolecular annulation of appropriately substituted 1,3-dicarbonyl compounds and their equivalents with hydroxylamine[4] or hydrazines.[5] Nevertheless, to match the increasing scientific and practical demand for isoxazoles and pyrazolin-5-ones, novel and efficient synthetic approach for the construction of these heterocyclic skeletons, especially those with wide applicability to achieve more elaborate and flexible substitution patterns, is still desirable.

On the other hand, cyclopropanes are extremely versatile synthetic intermediates for their ready accessibility and good reactivity originating from their inherent ring strain, which can lead to a variety of ring-opening or ring-expanding reactions under the influence of a wide range of chemicals, such as electrophiles, nucleophiles, and radicals.[6,7] During the course of our studies on the synthesis of carbo- and heterocycles from β-oxo amide derivatives,[8] we achieved one-pot synthesis of 2,3-dihydrofurans and pyridine-2(1*H*)-ones from 1-carbamoyl cyclopropanes.[9] Our recent researches have demonstrated the synthetic potential of 1-carbamoyl,1-oximyl cyclopropanes **1** in the construction of isoxazoles (Scheme 1, path A),[10] 1*H*-pyrazoles (Scheme 1, path B),[10] and spiro-fused pyrazolin-5-one *N*-oxides (Scheme 1, path C).[11]



Scheme 1. Reactions of 1-carbamoyl,1-oximyl cyclopropanes.

In connection with these studies and our continuing interest in the further synthetic potential of cyclopropyl oximes **1**, we examined their reactivity toward varied dehydration agents. As a result, we developed an efficient and divergent synthesis of isoxazoles **2** (Scheme 1, path D) and spiro-fused pyrazolin-5-ones **3** (Scheme 1, path E) under very mild conditions. Herein, we wish to report our experimental results and present proposed mechanisms involved in the ring-opening and/or cyclization reactions.

* Corresponding authors. Tel.: +86 431 85262190; fax: +86 431 85098635 (D.D.); tel./fax: +86 431 85262204 (G.Z.); e-mail addresses: gyzhou@ciac.jl.cn (G. Zhou), dongdw663@nenu.edu.cn (D. Dong).

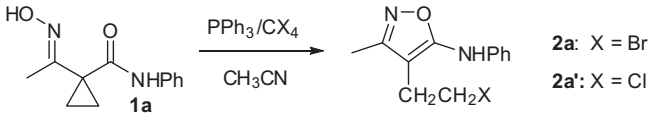
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.05.136

2. Results and discussion

2.1. Synthesis of fully substituted isoxazoles

Appel agents (PPh_3/CX_4, X=Cl, Br) have been extensively used in dehydration, halogenation, and P–N linking reactions.[12] Their efficient utilization in organic synthesis relies on their extremely mild reaction conditions required, easy handling, reactivity similar to aggressive, and readily hydrolyzed acid chlorides, such as PCl_5, $POCl_3$, and thionyl chloride. Recently, Shi and co-workers investigated the reactions of varied cyclopropyl amides with PPh_3/CX_4 and synthesized substituted benzoxazoles, pyrrolidin-2-ones, and oxadiazoles.[13]

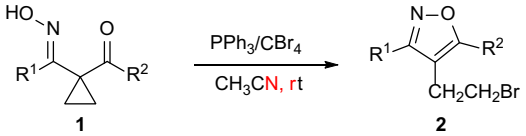
In the present work, the reaction of 1-[1-(hydroxyimino)ethyl]-N-phenylcyclopropanecarboxamide **1a** with PPh_3 (2.0 equiv) and CBr_4 (1.0 equiv) was first attempted in acetonitrile at room temperature. As indicated by TLC, the substrate **1a** was consumed within 20 min. The reaction proceeded smoothly and furnished one product after workup and purification by column chromatography. From the spectral and analytical data, the product was characterized as 4-(2-bromoethyl)-3-methyl-*N*-phenyl isoxazol-5-amine **2a** (89% yield, Scheme 2).



Scheme 2. The reaction of **1a** with PPh_3/CX_4.

The reaction conditions, including reaction temperature, solvent, and the ratio of **1a** to PPh_3 and CBr_4, were then investigated. A series of experiments revealed that 1.0 equiv of PPh_3 and CBr_4 were sufficient for the synthesis of **2a** and acetonitrile was the best solvent among those tested, and the optimal results were obtained when the reaction of **1a** was performed with PPh_3 (1.1 equiv) and CBr_4 (1.0 equiv) in acetonitrile at room temperature for 30 min, whereby the yield of **2a** reached 90% (Table 1, entry 1). It should be mentioned that when treatment of **1a** with PBr_3 in dichloromethane followed our previous reported procedure,[10] isoxazole **2a** could be obtained but in lower yield (<45%) along with some inseparable byproducts.

Table 1
The reactions of cyclopropyl oximes **1** with PPh_3/CBr_4[a]

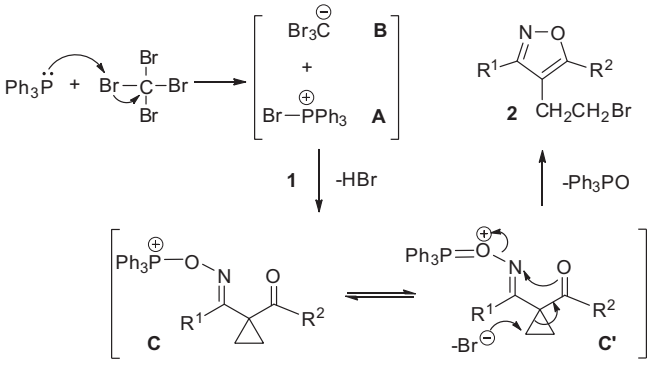


Entry	1	R^1	R^2	Time (min)	2	Yield[b] (%)
1	**1a**	Me	PhNH	30	**2a**	90
2	**1b**	Me	2-MeC_6H_4NH	40	**2b**	93
3	**1c**	Me	2-$MeOC_6H_4NH$	50	**2c**	91
4	**1d**	Me	4-MeC_6H_4NH	40	**2d**	94
5	**1e**	Me	4-$MeOC_6H_4NH$	35	**2e**	90
6	**1f**	Me	4-ClC_6H_4NH	50	**2f**	87
7	**1g**	Me	2,4-$Me_2C_6H_3NH$	50	**2g**	93
8	**1h**	Ph	EtO	300	**2h**	75

[a] Reagents and conditions: **1** (1.0 mmol), PPh_3 (1.1 mmol), CBr_4 (1.0 mmol), CH_3CN (5.0 mL), rt.
[b] Isolated yield.

Having established the optimal conditions for the isoxazole synthesis, we intended to determine its scope with respect to the amide motif. Thus, a series of cyclopropyl oximes **1b**–**g** were subjected to PPh_3/CBr_4 under the identical conditions, all the reactions proceeded smoothly to afford the corresponding isoxazoles **2** in good to excellent yields (Table 1, entries 2–7). As shown in Table 1, the ring-opening and cyclization reaction proved to be suitable for cyclopropyl oximes **1b**–**g** bearing varied arylamide groups. The versatility of this isoxazole synthesis was further evaluated by performing reaction of cyclopropyl ester **1h** with PPh_3/CBr_4 (Table 1, entry 8). In this case, the corresponding substituted isoxazole **2h** was obtained in good yield, albeit with prolonged reaction time. However, when **1a** was subjected to another Appel agent PPh_3/CCl_4 under the otherwise identical conditions, no reaction was observed as indicated by TLC. Upon treatment of **1a** with 1.5 equiv of PPh_3 and 1.0 equiv of CCl_4 under reflux for 10 h in acetonitrile, the reaction proceeded and furnished a product, which was characterized as 4-(2-chloroethyl)-3-methyl-*N*-phenyl isoxazol-5-amine **2a′** on the basis of its spectral and analytical data (85% yield, Scheme 2). Indeed, isoxazole **2a′** was synthesized in our previous work by the reaction of **1a** with $POCl_3$ in dichloromethane.[10] Therefore, we provided an alternative approach for the synthesis of substituted isoxazole of type **2**.

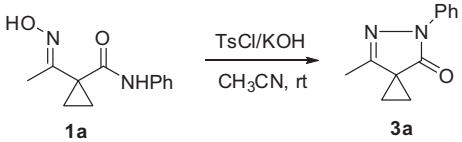
On the basis of the obtained results together with the related reports,[12f–i] a plausible mechanism for the synthesis of substituted isoxazoles **2** is presented in Scheme 3. The conversion involves the interaction of PPh_3 with CBr_4 to form the intermediate **A**, which reacts with cyclopropyl oxime **1** to produce an oxyphosphonium intermediate **C**. Bromide anion attacks the intermediate **C′** and triggers a ring-opening reaction and subsequent intramolecular cyclization to afford isoxazole **2** bearing a bromoethyl substituent, with elimination of triphenylphosphine oxide (Ph_3PO).



Scheme 3. Plausible mechanism of the reaction of cyclopropyl oximes **1** with PPh_3/CBr_4.

2.2. Synthesis of spiro-fused pyrazolin-5-ones

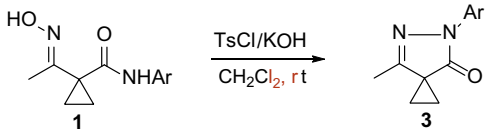
In the next study, we examined the reaction behavior of cyclopropyl oximes **1** toward another dehydration and halogenation agent, *p*-toluenesulfonyl chloride (TsCl).[14,15] The reaction of **1a** with TsCl (1.1 equiv) was then performed in acetonitrile in the presence of potassium hydroxide (2.0 equiv). As monitored by TLC, the substrate **1a** was consumed within 2.0 h. After workup and purification by column chromatography, the reaction furnished a white solid, which was characterized as 7-methyl-5-phenyl-5,6-diazaspiro[2.4]hept-6-en-4-one **3a** rather than an isoxazole on the basis of its spectral and analytical data (Scheme 4).[16]



Scheme 4. The reaction of **1a** with TsCl/KOH in CH_3CN.

The reaction conditions, including solvent, base, and the feed ratio of **1a**/TsCl/base were evaluated. After extensive experiments, the best results were obtained when the reaction between **1a** and TsCl (1.0 equiv) was conducted in dichloromethane in the presence of potassium hydroxide (2.0 equiv) at room temperature for 40 min, whereby the yield of **3a** reached 92% (Table 2, entry 1).

Table 2
The reaction of cyclopropyl oximes **1** with TsCl/KOH in CH_2Cl_2[a]



1 3

Entry	1	Ar	Time (min)	3	Yield[b] (%)
1	**1a**	Ph	40	**3a**[17]	92
2	**1b**	2-MeC_6H_4	60	**3b**	90
3	**1c**	2-$MeOC_6H_4$	75	**3c**	88
4	**1d**	4-MeC_6H_4	50	**3d**[17a]	93
5	**1e**	4-$MeOC_6H_4$	60	**3e**	91
6	**1f**	4-ClC_6H_4	80	**3f**[17a]	85
7	**1g**	2,4-$Me_2C_6H_3$	90	**3g**	91

[a] Reagents and conditions: **1** (1.0 mmol), KOH (2.0 mmol), TsCl (1.0 mmol), CH_2Cl_2 (10 mL), rt.
[b] Isolated yield.

Under the optimal conditions as for **3a** (Table 2, entry 1), a range of reactions of cyclopropyl oximes **1b**–**g** with TsCl (1.0 equiv) were carried out in the presence of potassium hydroxide (2.0 equiv) in CH_2Cl_2 at room temperature. As summarized in Table 2, the efficiency and synthetic interest of the cyclization reaction were demonstrated with respect to cyclopropyl oximes **1b**–**g** bearing varied electron-withdrawing and electron-donating arylamide groups to afford the corresponding spiro-fused pyrazolin-5-ones **3b**–**g**. The structure of **3e** was further confirmed by single-crystal X-ray diffraction analysis (Fig. 1). Thus, we provided an efficient and facile synthesis of spiro-fused pyrazolin-5-ones.

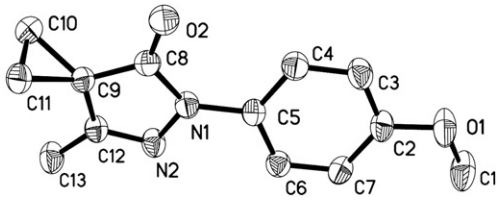
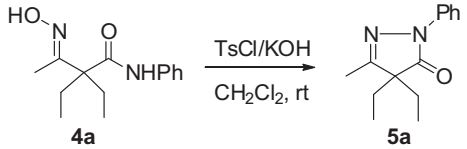


Fig. 1. The ORTEP drawing of **3e**.

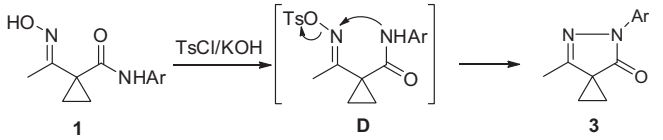
With the aim to exploring the utility of the pyrazolin-5-one synthesis protocol, we prepared acyclic oxime, 2,2-diethyl-3-(hydroxyimino)-*N*-phenylbutanamide **4a**, and subjected it to the identical conditions as for **3a** in Table 2 (entry 1). To our delighted, substituted pyrazolin-5-one **5a** was obtained in 82% yield (Scheme 5),[18] which suggested that the spiro-fused pyrazolin-5-one synthesis could be expanded to the synthesis of more general pyrazolin-5-ones with more elaborate and flexible substitution patterns.



4a 5a

Scheme 5. The reaction of oxime **4a** with TsCl/KOH in CH_2Cl_2.

It was interesting to note that TsCl, being a dehydration and halogenation agent, showed different reaction behavior from Appel reagent, PPh_3/CX_4. On the basis of the obtained results together with the related reports, a plausible mechanism for the synthesis of spiro-fused pyrazolin-5-ones **3** is depicted in Scheme 6. It was assumed that the transformation commenced from the tosylation of cyclopropyl oxime **1**, followed by an intramolecular cyclization of the intermediate **D** to afford spiro-fused pyrazolin-5-one **3** with the elimination of *p*-toluenesulfonic acid.



1 D 3

Scheme 6. Plausible mechanism of the reaction of cyclopropyl oximes **1** with TsCl/KOH in CH_2Cl_2.

3. Conclusions

In summary, an efficient and divergent synthesis of fully substituted isoxazoles **2** and spiro-fused pyrazolin-5-ones **3** has been developed from readily available 1-carbamoyl, 1-cyclopropyl oximes **1**. Under Appel conditions (PPh_3/CBr_4), oximes **1** were converted into isoxazoles **2** via a ring-opening and intramolecular cyclization process. Treatment of oximes **1** with *p*-toluenesulfonyl chloride in the presence of potassium hydroxide, spiro-fused pyrazolin-5-ones **3** were obtained via tandem ketoxime tosylation and intramolecular cyclization, which could be expanded to the synthesis of general pyrazolin-5-ones with more elaborate and flexible substitution patterns. The protocol is associated with readily available substrates, mild conditions, high yields, simple execution, and easy control of the reaction orientation by reaction conditions selection.

4. Experimental

4.1. General information

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, with TMS as internal standard at 25 °C. IR spectra (KBr) were recorded on FTIR-spectrophotometer in the range of 400–4000 cm^{-1}. Elemental analyses were carried out on a Perkin–Elmer PE-2400 analyzer.

4.2. Synthesis of fully substituted isoxazoles

*4.2.1. Typical procedure for the preparation of **2** (with **2a** as an example).* To a well-stirred solution of PPh_3 (1.1 mmol) and CBr_4 (1.0 mmol) in acetonitrile (5.0 mL), was added **1a** (1.0 mmol) in one portion. The reaction mixture was stirred at room temperature for 30 min. After **1a** was consumed (monitored by TLC), the resulting mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was washed with water (3×20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate=10:1) to give **2a** as a white solid (0.25 g, 90%).

*4.2.2. Physical data of compounds **2**.*

*4.2.2.1. 4-(2-Bromoethyl)-3-methyl-N-phenylisoxazol-5-amine (**2a**).* White solid: mp 136–138 °C; ^1H NMR (500 MHz, $CDCl_3$) δ=2.23 (s, 3H), 2.86 (t, *J*=7.0, 2H), 3.43 (t, *J*=7.0, 2H), 6.42 (s, 1H),

7.02 (t, J=7.5, 1H), 7.12 (d, J=8.0, 2H), 7.29–7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.6, 25.8, 32.4, 95.0, 117.2, 122.3, 129.4, 139.7, 160.6, 162.5; IR (KBr) 3296, 3206, 3110, 3041, 2966, 2925, 1648, 1589, 1530, 1480, 1304, 1225, 1173, 751, 706 cm^{-1}; Anal. Calcd for $C_{12}H_{13}BrN_2O$: C, 51.26; H, 4.66; N, 9.96. Found: C, 51.34; H, 4.69; N, 9.94.

*4.2.2.2. 4-(2-Bromoethyl)-3-methyl-N-o-tolylisoxazol-5-amine (**2b**).* White solid: mp 83–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.22 (s, 3H), 2.29 (s, 3H), 2.83 (t, J=6.5, 2H), 3.42 (t, J=6.5, 2H), 6.25 (s, 1H), 6.96–6.99 (m, 1H), 7.16–7.19 (m, 2H), 7.22 (d, J=8.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.6, 17.8, 25.9, 33.0, 95.3, 117.9, 122.9, 126.3, 127.1, 130.8, 138.0, 160.7, 163.0; Anal. Calcd for $C_{13}H_{15}BrN_2O$: C, 52.90; H, 5.12; N, 9.49. Found: C, 53.01; H, 5.14; N, 9.45.

*4.2.2.3. 4-(2-Bromoethyl)-N-(2-methoxyphenyl)-3-methyl isoxazol-5-amine (**2c**).* White solid: mp 85–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.22 (d, J=1.0, 3H), 2.88 (t, J=6.5, 2H), 3.45 (t, J=6.5, 2H), 3.91 (d, J=1.5, 3H), 6.87–6.89 (m, 1H), 6.92–6.96 (m, 2H), 7.00 (s, 1H), 7.53 (dd, J_1=6.5, J_2=2.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.6, 25.9, 32.3, 55.8, 94.4, 110.2, 115.6, 121.3, 121.7, 129.3, 147.1, 160.3, 162.6; IR (KBr) 3388, 3073, 3018, 2967, 2931, 1649, 1598, 1528, 1462, 1244, 1114, 1027, 744 cm^{-1}; Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.27; H, 4.91; N, 8.96.

*4.2.2.4. 4-(2-Bromoethyl)-3-methyl-N-p-tolylisoxazol-5-amine (**2d**).* White solid: mp 141–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.21 (s, 3H), 2.30 (s, 3H), 2.83 (t, J=7.0, 2H), 3.40 (t, J=7.0, 2H), 6.44 (s, 1H), 7.03–7.04 (m, 2H), 7.10 (d, J=8.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.5, 20.6, 25.8, 32.3, 94.0, 117.7, 129.9, 132.1, 137.0, 160.6, 162.9; IR (KBr) 3285, 3204, 3091, 3033, 2991, 2943, 1643, 1589, 1519, 1480, 1236, 816 cm^{-1}; Anal. Calcd for $C_{13}H_{15}BrN_2O$: C, 52.90; H, 5.12; N, 9.49. Found: C, 52.78; H, 5.13; N, 9.55.

*4.2.2.5. 4-(2-Bromoethyl)-N-(4-methoxyphenyl)-3-methyl isoxazol-5-amine (**2e**).* White solid: mp128–129 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.20 (s, 3H), 2.80 (t, J=7.0, 2H), 3.37 (t, J=7.0, 2H), 3.80 (s, 3H), 6.34 (s, 1H), 6.86 (d, J=9.0, 2H), 7.10 (d, J=9.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.6, 25.8, 32.4, 55.6, 92.7, 114.6, 120.4, 132.4, 155.7, 160.7, 163.3; IR (KBr) 3294, 3209, 3101, 2969, 2833, 1643, 1592, 1511, 1491, 1247, 1035, 824 cm^{-1}; Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.30; H, 4.82; N, 8.93.

*4.2.2.6. 4-(2-Bromoethyl)-N-(4-chlorophenyl)-3-methylisoxazol-5-amine (**2f**).* White solid: mp 113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.22 (s, 3H), 2.87 (t, J=6.0, 2H), 3.44 (t, J=6.0, 2H), 6.64 (s, 1H), 7.07 (d, J=8.0, 2H), 7.24 (d, J=8.0, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.5, 25.7, 32.5, 95.3, 118.3, 127.2, 129.3, 138.4, 160.6, 162.1; IR (KBr) 3287, 3218, 3099, 3028, 2989, 1642, 1517, 1484, 1466, 1401, 1303, 1230, 820, 798 cm-1; Anal. Calcd for $C_{12}H_{12}BrClN_2O$: C, 45.67; H, 3.83; N, 8.88. Found: C, 45.52; H, 3.79; N, 8.97.

*4.2.2.7. 4-(2-Bromoethyl)-N-(2,4-dimethylphenyl)-3-methyl isoxazol-5-amine (**2g**).* White solid: mp 114–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.20 (s, 3H), 2.25 (s, 3H), 2.29 (s, 3H), 2.78 (t, J=6.5, 2H), 3.37 (t, J=6.5, 2H), 6.13 (s, 1H), 6.98 (d, J=8.0, 1H), 7.00 (s, 1H), 7.12 (d, J=8.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=10.6, 17.8, 20.7, 25.9, 32.9, 93.9, 119.3, 127.5, 131.5, 133.1, 135.1, 160.8, 163.4; Anal. Calcd for $C_{14}H_{17}BrN_2O$: C, 54.38; H, 5.54; N, 9.06. Found: C, 54.48; H, 5.59; N, 8.98.

*4.2.2.8. 4-(2-Bromoethyl)-5-ethoxy-3-phenylisoxazole (**2h**).* Colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.44 (t, J=7.0, 3H), 3.04 (t, J=7.0, 2H), 3.65 (t, J=7.0, 2H), 4.30 (q, J=7.0, 2H), 7.40–7.44 (m, 3H), 7.90–7.92 (dd, J_1=8.0, J_2=1.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=15.1, 28.8, 30.9, 70.6, 115.4, 125.4, 127.6, 128.7, 129.7, 152.6, 154.9; Anal. Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.55; H, 4.77; N, 4.68.

4.3. Synthesis of spiro-fused pyrazolin-5-ones

*4.3.1. Typical procedure for the preparation of **3** (with **3a** as an example).* To a 50 mL round-bottomed flask was added CH_2Cl_2 (10 mL), **1a** (1.0 mmol) and KOH (2.0 mmol). The mixture was stirred at room temperature for 10 min, to which was then added tosyl chloride (1.0 mmol). The reaction mixture was stirred at room temperature for 30 min. After **1a** was consumed (monitored by TLC), the resulting mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was washed with water (3×20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate=8:1) to give **3a** as a white solid (0.18 g, 92%).

*4.3.2. Physical data of compounds **3**.*

*4.3.2.1. 7-Methyl-5-phenyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**3a**).* White solid: mp 71–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.66–1.68 (m, 2H), 1.77–1.79 (m, 2H), 1.98 (s, 3H), 7.17 (t, J=7.5, 1H), 7.39–7,42 (m, 2H), 7.92–7.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=12.5, 18.7, 33.7, 118.6, 124.7, 128.7, 138.6, 159.8, 172.4; IR (KBr) 3389, 3009, 2953, 2917, 1964, 1707, 1592, 1502, 1456, 1362, 1176, 984, 758, 715, 690 cm^{-1}; Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.83; H, 6.10; N, 14.07.

*4.3.2.2. 7-Methyl-5-o-tolyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**3b**).* White solid: mp 54–55 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.65–1.67 (m, 2H), 1.75–1.77 (m, 2H), 1.93 (s, 3H), 2.28 (s, 3H), 7.24–7.28 (m, 3H), 7.32–7.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=12.6, 18.4, 18.5, 32.5, 126.5, 126.6, 128.2, 131.0, 135.1, 136.3, 159.6, 172.9; Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.96; H, 6.54; N, 13.12.

*4.3.2.3. 5-(2-Methoxyphenyl)-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**3c**).* White solid: mp 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.67 (t, J=4.0, 2H), 1.78 (t, J=4.0, 2H), 1.96 (s, 3H), 3.85 (s, 3H), 7.00–7.02 (m, 2H), 7.34–7.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=12.5, 18.4, 32.3, 55.8, 112.2, 120.6, 126.0, 128.4, 129.6, 154.9, 159.3, 173.3; IR (KBr) 3388, 3090, 3076, 2969, 2920, 2841, 1909, 1706, 1596, 1503, 1468, 1381, 1278, 1244, 1176, 1122, 1107, 757, 742 cm^{-1}; Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.94; H, 6.17; N, 12.12.

*4.3.2.4. 7-Methyl-5-p-tolyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**3d**).* White solid: mp 102–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.63–1.66 (m, 2H), 1.74–1.77 (m, 2H), 1.97 (s, 3H), 2.34 (s, 3H), 7.20 (d, J=8.5, 2H), 7.79 (d, J=8.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=12.6, 18.7, 20.9, 33.7, 118.7, 129.3, 134.3, 136.3, 159.7, 172.3; IR (KBr) 2992, 2918, 2861, 1918, 1697, 1612, 1516, 1445, 1362, 1170, 983, 852 cm^{-1}; Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.75; H, 6.67; N, 13.16.

*4.3.2.5. 5-(4-Methoxyphenyl)-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**3e**).* White solid: mp 71–72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.66 (t, J=4.0, 2H), 1.75 (t, J=4.0, 2H), 1.96 (s, 3H), 3.81 (s, 3H), 6.92–6.94 (m, 2H), 7.79–7.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=12.4, 18.6, 33.5, 55.3, 113.8, 120.4, 132.0, 156.6, 159.6, 172.0; IR (KBr) 3107, 3018, 2960, 2930, 2837, 1895, 1689, 1601, 1578, 1508, 1445, 1360, 1294, 1248, 1166, 1031, 989, 835 cm^{-1}; Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.93; H, 6.08; N, 12.23. Crystal data: $C_{13}H_{14}N_2O_2$.

Colorless crystal, M=230.11, Orthorhombic, *Pbca*, a=8.4987(7) Å, b=12.3021(10) Å, c=22.5908(17) Å, α=90.00°, β=90.00°, γ=90.00°, V=2361.9(3) Å^3, Z=8, T=293(2), F_{000}=1024, R_1=0.0638, wR_2=0.1278. CCDC deposition number: 781729. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk).

*4.3.2.6. 5-(4-Chlorophenyl)-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**3f**).* White solid: mp 121–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.68 (t, J=4.0, 2H), 1.77 (t, J=4.0, 2H), 1.98 (s, 3H), 7.34–7.36 (m, 2H), 7.90–7.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=12.6, 18.9, 33.8, 119.6, 128.8, 129.6, 137.3, 160.1, 172.4; IR (KBr) 3086, 3055, 2952, 2916, 2849, 1908, 1695, 1606, 1592, 1492, 1448, 1358, 1177, 1133, 1088, 981, 841, 816 cm^{-1}; Anal. Calcd for $C_{12}H_{11}ClN_2O$: C, 61.41; H, 4.72; N, 11.94. Found: C, 61.28; H, 4.64; N, 11.88.

*4.3.2.7. 5-(2,4-Dimethylphenyl)-7-methyl-5,6-diazaspiro[2.4]hept-6-en-4-one (**3g**).* White solid: mp 76–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.65–1.67 (m, 2H), 1.76–1.78 (m, 2H), 1.95 (s, 3H), 2.23 (s, 3H), 2.33 (s, 3H), 7.05 (d, J=8.0, 1H), 7.09 (s, 1H), 7.20 (d, J=8.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=12.6, 18.2, 18.4, 21.1, 32.5, 126.6, 127.2, 131.7, 133.8, 134.9, 138.1, 159.4, 173.0; Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.79; H, 7.09; N, 12.23.

*4.3.2.8. 2,2-Diethyl-3-(hydroxyimino)-N-phenylbutanamide (**4a**).* White solid, mp: 135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=0.81 (t, J=7.6, 6H), 1.86–2.02 (m, 7H), 7.12 (t, J=8.0, 1H), 7.31 (t, J=8.0, 2H), 7.50 (d, J=8.0, 2H), 8.13 (s, 1H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=8.4, 11.5, 24.9, 58.1, 120.2, 124.4, 128.9, 137.6, 159.7, 171.4; Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.55; H, 8.31; N, 11.36.

*4.3.2.9. 4,4-Diethyl-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**5a**).* ^{1}H NMR (600 MHz, $CDCl_3$) δ=0.85 (t, J=7.2, 6H), 1.70–1.74 (m, 2H), 1.89–1.92 (m, 2H), 1.99 (s, 3H), 7.10 (t, J=7.2, 1H), 7.15 (d, J=7.2, 2H), 7.32 (t, J=7.2, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ=8.8, 10.6, 29.6, 60.4, 122.6, 124.2, 128.6, 145.7, 163.7, 165.6; Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 73.31; H, 7.61; N, 12.34.

Acknowledgements

Financial support of this research by the National Natural Science Foundation of China (20872136 and 51073150) is greatly acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.05.136.

References and notes

1. Balkenhohl, F.; Von Dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2288–2337; (b) Dolle, R. E. *J. Comb. Chem.* **2004**, *6*, 623–679; (c) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012–3043.
2. (a) Carlsen, L.; Döpp, D.; Döpp, H.; Duus, F.; Hartmann, H.; Lang-Fugmann, S.; Schulze, B.; Smalley, R. K.; Wakefield, B. J. In *Houben–Weyl, Methods in Organic Chemistry*; Schaumann, E., Ed.; Georg Thieme: Stuttgart, Germany, 1992; Vol E8a, pp 45–204; (b) Makaritis, A.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Chem.—Eur. J.* **2003**, *9*, 2079–2094; (c) Lilienkampf, A.; Mao, J.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2009**, *52*, 2109–2118; (d) Lilienkampf, A.; Pieroni, M.; Wan, B.; Wang, Y.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2010**, *53*, 678–688; (e) Mao, J.; Yuan, H.; Wang, Y.; Wan, B.; Pak, D.; He, R.; Franzblau, S. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1263–1268; (f) Dallanoce, C.; Frigerio, F.; De Amici, M.; Dorsch, S.; Klotz, K.-N.; De Micheli, C. *Bioorg. Med. Chem.* **2007**, *15*, 2533–2543.
3. (a) Castagnolo, D.; Manetti, F.; Radi, M.; Bechi, B.; Pagano, M.; De Logu, A.; Meleddu, R.; Saddi, M.; Botta, M. *Bioorg. Med. Chem.* **2009**, *17*, 5716–5721; (b) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053–5056; (c) Chande, M. S.; Barve, P. A.; Suryanarayan, V. *J. Heterocycl. Chem.* **2007**, *44*, 49–53; (d) Shelke, S. N.; Dalvi, N. R.; Kale, S. B.; More, M. S.; Gill, C. H.; Karale, B. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2007**, *46*, 1174–1178; (e) Sogawa, Y.; Shimizugawa, A.; Ohyama, T.; Maeda, H.; Hirahara, K. *J. Pharmacol. Sci.* **2009**, *111*, 317–321.
4. For the synthesis of isoxazoles, see: (a) Lautens, M.; Roy, A. *Org. Lett.* **2000**, *2*, 555–557; (b) Savant, M. M.; Pansuriya, A. M.; Bhuva, C. V.; Kapuriya, N.; Patel, A. S.; Audichya, V. B.; Pipaliya, P. V.; Naliapara, Y. T. *J. Comb. Chem.* **2010**, *12*, 176–180; (c) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203–5205; (d) Barr, L.; Lincoln, S. F.; Easton, C. J. *Chem.—Eur. J.* **2006**, *12*, 8571–8580; (e) Grecian, S.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 8285–8287.
5. For the synthesis of pyrazolin-5-ones, see: (a) Tietze, L. F.; Evers, H.; Hippe, T.; Steinmetz, A.; Töpken, E. *Eur. J. Org. Chem.* **2001**, 1631–1634; (b) Attanasi, O. A.; Baccolini, G.; Boga, C.; De Crescentini, L.; Giorgi, G.; Mantellini, F.; Nicolini, S. *Eur. J. Org. Chem.* **2008**, 5965–5973; (c) Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Foresti, E.; Mantellini, F. *J. Org. Chem.* **2000**, *65*, 2820–2823.
6. For reviews, see: (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72; (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C. *Chem. Rev.* **1989**, *89*, 165–198; (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196; (d) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150; (e) Reichelt, A.; Martin, S. F. *Acc. Chem. Res.* **2006**, *39*, 433–442.
7. For selected examples, see: (a) Korotkov, V. S.; Larionov, O. V.; Hofmeister, A.; Magull, J.; De Merjere, A. *J. Org. Chem.* **2007**, *72*, 7504–7510; (b) Tanaka, M.; Ubakata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331–3334; (c) Morales, C. L.; Pagenkopf, B. L. *Org. Lett.* **2008**, *10*, 157–159; (d) Tsuritani, T.; Yamamoto, Y.; Kawasaki, M.; Mase, T. *Org. Lett.* **2009**, *11*, 1043–1045; (e) Hours, A. E.; Snyder, J. K. *Organometallics* **2008**, *27*, 410–417.
8. (a) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579; (b) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580–3582; (c) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593–8596; (d) Xiang, D.; Huang, P.; Wang, K.; Zhou, G.; Liang, Y.; Dong, D. *Chem. Commun.* **2008**, 6236–6238; (e) Xiang, D.; Wang, K.; Liang, Y.; Zhou, G.; Dong, D. *Org. Lett.* **2008**, *10*, 345–348; (f) Zhang, R.; Zhang, D.; Guo, Y.; Zhou, G.; Jiang, Z.; Dong, D. *J. Org. Chem.* **2008**, *73*, 9504–9507; (g) Wang, Y.; Xin, X.; Liang, Y.; Lin, Y.; Duan, H.; Dong, D. *Adv. Synth. Catal.* **2009**, *351*, 2217–2223.
9. (a) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421–2423; (b) Zhang, R.; Liang, Y.; Zhou, G.; Wang, K.; Dong, D. *J. Org. Chem.* **2008**, *73*, 8089–8092.
10. Wang, K.; Xiang, D.; Liu, J.; Pan, W.; Dong, D. *Org. Lett.* **2008**, *10*, 1691–1694.
11. Wang, K.; Fu, X.; Liu, J.; Liang, Y.; Dong, D. *Org. Lett.* **2009**, *11*, 1015–1018.
12. For review, see: (a) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811; (b) For the use of Ph_3P/CCl_4, see: Das, B.; Kanth, B. S.; Reddy, K. R.; Satyalakshmi, G.; Kumar, R. A. *Chem. Lett.* **2008**, *37*, 512–513; (c) Ori, M.; Toda, N.; Takami, K.; Tago, K.; Kogen, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2540–2543; (d) Wang, Z.; Wan, W.; Jiang, H.; Hao, J. *J. Org. Chem.* **2007**, *72*, 9364–9367; (e) Morwick, T.; Hrapchak, M.; De Turi, M.; Campbell, S. *Org. Lett.* **2002**, *4*, 2665–2668; (f) For the use of Ph_3P/CBr_4, see: Das, B.; Damodar, K.; Bhunia, N.; Shashikanth, B. *Tetrahedron Lett.* **2009**, *50*, 2072–2074; (g) Gouin, S. G.; Kovensky, J. *Tetrahedron Lett.* **2007**, *48*, 2875–2879; (h) Yadav, J. S.; Mishra, R. K. *Tetrahedron Lett.* **2002**, *43*, 5419–5422; (i) Nishida, Y.; Shingu, Y.; Dohi, H.; Kobayashi, K. *Org. Lett.* **2003**, *5*, 2377–2380.
13. (a) Yang, Y.-H.; Shi, M. *Tetrahedron* **2006**, *62*, 2420–2427; (b) Yang, Y.-H.; Shi, M. *J. Org. Chem.* **2005**, *70*, 8645–8648; (c) Yang, Y.-H.; Shi, M. *Tetrahedron Lett.* **2005**, *46*, 6285–6288.
14. For chlorination, see: (a) Brummond, K. M.; Gesenberg, K. D. *Tetrahedron Lett.* **1999**, *40*, 2231–2234; (b) Lai, G.; Tan, P.-Z.; Ghoshal, P. *Synth. Commun.* **2003**, *33*, 1727–1732; (c) Nair, R. P.; Kim, T. H.; Frost, B. J. *Organometallics* **2009**, *28*, 4681–4688.
15. For dehydration, see: (a) Khalafi-Nezhad, A.; Parhami, A.; Rad, M. N. S.; Zarea, A. *Tetrahedron Lett.* **2005**, *46*, 6879–6882; (b) Kazemi, F.; Sharghi, H.; Nasseri, M. A. *Synthesis* **2004**, 205–207; (c) Pirrung, M. C.; Tumey, L. N. *J. Comb. Chem.* **2000**, *2*, 675–680; (d) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*, 1209–1214; (e) Katritzky, A. R.; Wang, M.; Wilkerson, C. R.; Yang, H. *J. Org. Chem.* **2003**, *68*, 9105–9108; (f) Dale, T. J.; Sather, A. C., Jr. *Tetrahedron Lett.* **2009**, *50*, 6173–6175.
16. For the synthesis of spiro-fused pyrazolin-5-ones, see: (a) Corce, P. D.; Pocar, D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 620–622; (b) Ren, Z.; Cao, W.; Chen, J.; Chen, Y.; Deng, H.; Shao, M.; Wu, D. *Tetrahedron* **2008**, *64*, 5156–5161; (c) Alba, A. N. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2011**, 1318–1325; (d) Sammelson, R. E.; Gurusinghe, C. D.; Kurth, J. M.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 876–882; (e) Holzer, W.; Claramunt, R. M.; Perez-Torralba, M.; Guggi, D.; Brehmer, T. H. *J. Org. Chem.* **2003**, *68*, 7943–7950.
17. (a) Wamhoff, H.; Atta, S. M. S. *Chem.-Ztg.* **1984**, *108*, 285–286; (b) Wamhoff, H.; Korte, F. *Chem. Ber.* **1966**, *99*, 2962–2970; (c) Magnien, E.; Tom, W. *J. Org. Chem.* **1967**, *32*, 1229–1230.
18. For the preparation of **5a** from hydrazine and its analytical data, see: Auwers, K. V.; Dersch, F. *Justus Liebigs Ann. Chem.* **1928**, *462*, 104–134.