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Report

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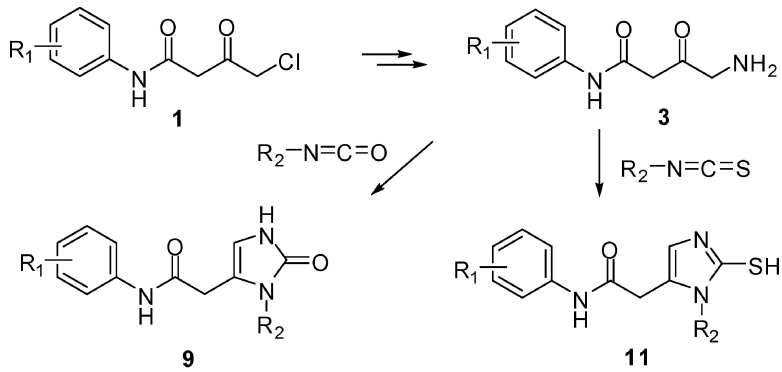

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Reports

Syntheses of 1,3-Imidazolin-2-Ones and 1,3-Imidazolin-2-Thiones from New Building Blocks, γ-Aminoacetoacetanilides

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Exploration of new building blocks for the preparation of heterocyclic compound libraries with molecular diversity is an ever-expanding area in combinatorial chemistry. To respond to this demand, new technologies, including multicomponent reactions[1] and click chemistry,[2] have been developed. In our previous paper,[3] we reported that the construction of two different chemical libraries of 1,3-imidazolin-2-thione and 2-phenylimino-1,3-thiazoline starting from three building blocks, γ-chloroacetoacetanilides **1**, amines, and isothiocyanates. As an expansion of our study for the construction of a new chemical library of heterocyclic compounds, we synthesized new γ-aminoacetoacetanilide derivatives **3** by replacing chlorine in **1** with amino moiety. The γ-aminoacetoacetanilide derivatives **3** would be useful building blocks for preparing new heterocyclic compounds because of their four reactive centers within the molecule. First, the methylene protons are activated by neighboring carbonyl moieties. Second, the amide is an ambient nucleophile by means of the nitrogen and oxygen atoms. Third, the carbonyl of the ketone is susceptive for an addition of nucleophile. Fourth, the primary amine at γ position has good nucleophilic character.

In this paper, we report the synthesis of the new building blocks, γ-aminoacetoacetanilide derivatives **3** and the preparations of two different scaffolds, 1,3-imidazolin-2-one **9** and 1,3-imidazolin-2-thione derivatives **10**, by the reaction of **3** with isocyanates and isothiocyanates, respectively.

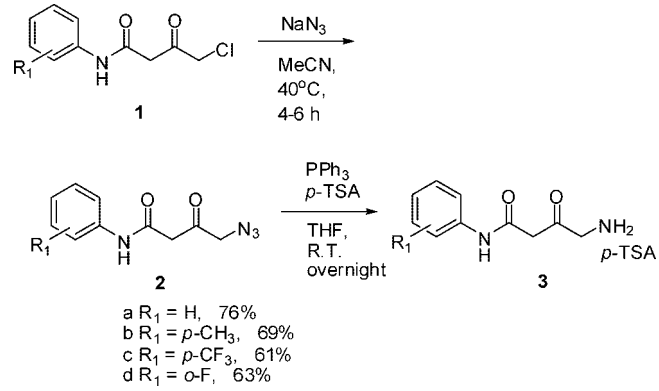
1,3-Imidazolin-2-one and its sulfur analogue, 1,3-imidazolin-2-thione, derivatives have received attention over the past few years because of their interesting biological activities.[4,5] For example, enoximone and piroximone possess antioxidant, phosphodiesterase, and cardiotonic activities.[6] Others have been shown to exhibit good herbicidal activities, such as imazamethbenz and imazethapyr.[7] There are many known methods for the synthesis of 1,3-imidazolin-2-ones and 1,3-imidazolin-2-thiones, including Marckwald's method.[8] Recently, the novel synthesis of imidazolin-2-thiones was reported by Zeng et al., and their use in organic synthesis was reviewed by Zav'yalov et al.[9,10]

The starting γ-chloroacetoacetanilides **1** were prepared by the same method as previously reported.[3] α-Aminoketones are considerably less well behaved for organic syntheses, as compared to α-aminoesters, because of self-condensation reactions. As shown in Scheme 1, the γ-aminoacetoacetanilides **3** can be prepared easily and efficiently from **1** through a modified procedure of the previously reported method.[11] The reaction of γ-chloroacetoacetanilides **1** with sodium azide in acetonitrile at 40° for 4−6 h gave γ-azidoketone **2** in a quantitative yield. The same reaction at a higher temperature or longer reaction time resulted in low yield of the product. Without purification, treatment of **2** with triphenylphosphine in tetrahydrofuran in the presence of excess amount (3 mol equiv) of *p*-toluenesulfonic acid monohydrate (*p*-TSA) at room temperature afforded γ-aminoacetoacetanilides **3** as the *p*-TSA salts. The structure of **3** was confirmed by the ^{1}H NMR spectroscopy and the IR spectrometry. For **3a**, two singlets at δ 3.71 and 4.08 ppm in the ^{1}H NMR spectrum and a strong absorption at 3200−3300 cm^{-1} in the IR spectra were in agreement with the structure.

After the supply of **3** was secured, the chemical reactivity and available potentialities for the construction of heterocyclic molecules from **3** were investigated. Because the γ-amino moiety in **3** is a good nucleophile, we decided to react **3** with a good electrophile, such as isocyanate derivatives. The reaction between **3b** and *o*-tolyl isocyanate, which was chosen arbitrarily, proceeded smoothly in the presence of triethylamine at room temperature for 2 h to obtain the desired product **5b** (Scheme 2). Acetone was the best solvent of choice for obtaining high yield of **5b**. Solvents such as acetonitrile, benzene, methylene chloride, dioxane, dimethylformamide, or ethanol either gave poor yields of **5b** or led to the production of side products.

Under similar reaction conditions, the γ-aminoacetoacetanilides **3** were subjected to various isocyanate or isothio-

Scheme 1. Syntheses of γ-Aminoacetoacetanilides **3**



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Scheme 2. Conversion of γ-Aminoacetoacetanilide **3b** to **5b**

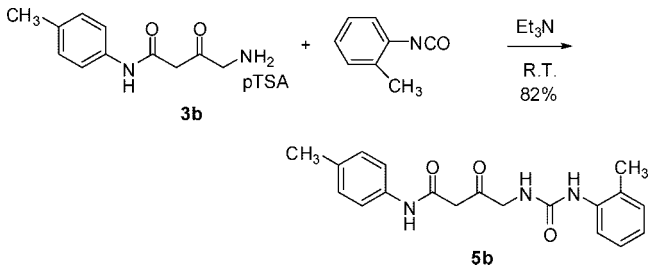


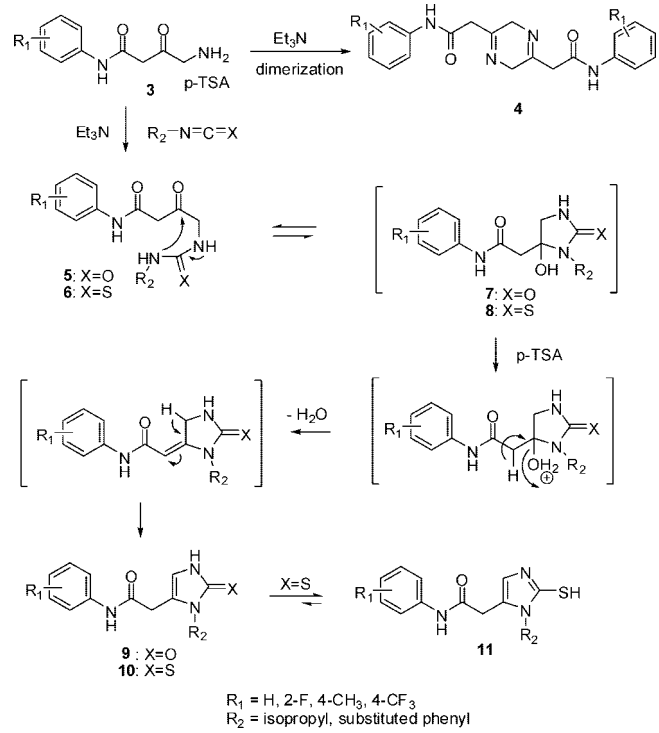
Table 1. Melting Points and the Yields of Ureas **5** and Thioureas **6**

compounds	R_1	R_2	X	mp (°C)	yield (%)[a]
5a	H	$CH(CH_3)_2$	O	137	80
5b	H	$C_6H_5(2\text{-}CH_3)$	O	149	82
5c	H	$C_6H_5(4\text{-}OCH_3)$	O	*b*	*b*
5d	4-CH_3	$CH(CH_3)_2$	O	148	61
5e	4-CH_3	$C_6H_5(2\text{-}CH_3)$	O	164	84
5f	4-CH_3	$C_6H_5(4\text{-}OCH_3)$	O	*b*	*b*
5g	4-CF_3	$CH(CH_3)_2$	O	163	50
5h	4-CF_3	$C_6H_5(2\text{-}CH_3)$	O	163	79
5i	4-CF_3	$C_6H_5(4\text{-}OCH_3)$	O	209	81
5j	2-F	$CH(CH_3)_2$	O	176	66
5k	2-F	$C_6H_5(2\text{-}CH_3)$	O	146	71
5l	2-F	$C_6H_5(4\text{-}OCH_3)$	O	200	68
6a	H	$C_6H_5(3,5\text{-diCl})$	S	161	61
6b	H	$C_6H_5(4\text{-}NO_2)$	S	187	66
6c	4-CH_3	$C_6H_5(3,5\text{-diCl})$	S	153	53
6d	4-CH_3	$C_6H_5(4\text{-}NO_2)$	S	147	62
6e	4-CF_3	$C_6H_5(3,5\text{-diCl})$	S	154	62
6f	4-CF_3	$C_6H_5(4\text{-}NO_2)$	S	132	58
6g	2-F	$C_6H_5(3,5\text{-diCl})$	S	236	54
6h	2-F	$C_6H_5(4\text{-}NO_2)$	S	176	56

[a] Determined by HPLC chromatography detection at 254 nm for X = O, whereas the yields were isolated yield for X = S. [b] These compounds underwent simultaneous cyclization under the reaction conditions to give the corresponding 1,3-imidazolin-2-ones **9**.

cyanate derivatives in the presence of triethylamine and were held at room temperature in acetone to afford moderate yields (43−84%) of the corresponding ureas **5** or thioureas **6** (Table 1). As shown in Scheme 3, the nucleophilic addition of amino nitrogen of **3** to the carbon of isocyanate or isothiocyanate took place initially to give **5** or **6**, respectively. From this reaction, a small amount of (less than 10%) **4**, a dimer of **3** by self-condensation of γ-aminoacetoacetanilide, was formed. Although the dimer **4** was unstable under the reaction condition (judged by TLC), it could be isolated by filtration from the reaction mixture after a short reaction time. However, no increased yield of urea **5** was obtained when an excess (5 mol equiv) amount of isocyanate derivative was used under the same reaction conditions. Some ureas **5** (for instance, **5c** and **5f**, in which electron-donating methoxy group was substituted at para position) were converted spontaneously to the corresponding 1,3-imidazolin-2-ones. In the case of the isothiocyanates, the thioureas **6** were isolated as solids by filtration from the reaction mixture in a moderate yield (53−62%) after the reaction without further purification process. The structures of the urea **5** and the thiourea **6** were identified by their ^{1}H NMR spectroscopy. For the ureas **5**, a singlet in a range of δ 3.5−3.7 for methylene protons adjacent to two carbonyls, and a doublet (J = 11−12 Hz) in a range of δ 3.9−4.1 for other methylene protons adjacent to the nitrogen, appeared in their ^{1}H NMR spectra. The thiourea **6** existed as their closed form **8**, which

Scheme 3. Reactions of γ-Aminoacetoacetanilides **3** with Isocyanates and Isothiocyanates



was determined by their ^{1}H NMR spectroscopy. Two typical doublets (J = 14 Hz) of the AB splitting pattern at δ 4.2 and 3.6 for C-4 protons in the 1,3-imidazolin-2-thione ring and the signals of the same fashion at δ 2.7 and 2.66 for methylene protons adjacent to the carbonyl were agreement with the structure **8**.

Treatment of **5** and **6** with an acid catalyst (*p*-TSA) in refluxing benzene for a short reaction time gave the corresponding imidazolin-2-one **9** and imidazolin-2-thione **10** via intermediate **7** or **8**, respectively. The structures of the 1,3-imidazolin-2-one **9** and **10** were characterized by their ^{1}H NMR spectral data. The vinyl proton at C-5 of the 1,3-imidazolin-2-one **9** resonated with the adjacent NH to show the doublet (J = 1−2 Hz) in DMSO-d_6. In fact, the 1,3-imidazolin-3-thione **10** existed as a more stable form mercaptoimidazole **11**, determined by their ^{1}H NMR spectroscopy. Thus, the vinyl proton at C-5 of the **11** showed a singlet at 6.99 ppm and thiol proton resonates at 12.42 ppm.[12] In the case of thiourea **6**, nucleophilic addition would take place at the two reactive centers of the thioamide,[13] which could undergo further transformation to provide either 1,3-imidazolin-2-thione **10** or 1,3-thiazole derivative (see Supporting Information), depending on whether the nitrogen or sulfur of the thiourea moiety acts as the nucleophile. Since the spectral data (e.g., ^{1}H and ^{13}C NMR, HMQC, HMBC, IR and MS) were not conclusive to confirm the structure, we decided to obtain NOESY correlation data.

The NOE correlations observed between H_b and H_c prevailed to produce 1,3- mercaptoimidazole **11c** (Figure 1). In addition, the correlations between H_a and thiol proton and H_b and NH proton were shown from the NOESY spectrum. Further proof of the correct structure was provided by its conversion to **12**, as shown in Scheme 4. The mercaptoimidazole **11c** was subjected to ethyl 4-chloroacetoacetate in the presence of

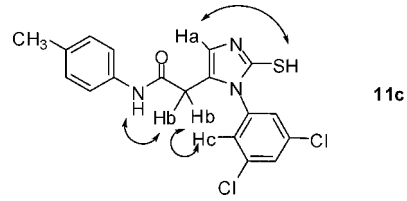


Figure 1. Selected NOE correlations observed for **11c**.

Scheme 4. Conversion of Mercaptoimidazole **11c** to Sulfide **12**.

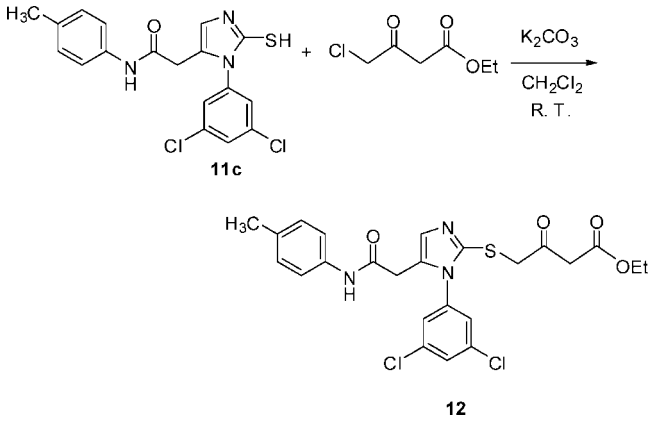


Table 2. List of Compounds **9** and **11** and their Melting Points and Yields

compounds	R_1	R_2	X	mp (°C)	yields (%)[a]
9a	H	$CH(CH_3)_2$	O	196	49
9b	H	C_6H_5(2-CH_3)	O	110	82
9c	H	C_6H_5(4-OCH_3)	O	202	73
9d	4-CH_3	$CH(CH_3)_2$	O	195	42
9e	4-CH_3	C_6H_5(4-OCH_3)	O	218	84
9f	4-CF_3	$CH(CH_3)_2$	O	219	28
9g	4-CF_3	C_6H_5(4-OCH_3)	O	198	71
9h	2-F	$CH(CH_3)_2$	O	194	61
11a	H	C_6H_5(3,5-di Cl)	S	194	46
11b	H	C_6H_5(4-NO_2)	S	196	95
11c	4-CH_3	C_6H_5(3,5-di Cl)	S	195	70
11d	4-CH_3	C_6H_5(4-NO_2)	S	170	61
11e	4-CF_3	C_6H_5(3,5-di Cl)	S	213	69
11f	4-CF_3	C_6H_5(4-NO_2)	S	170	22
11g	2-F	C_6H_5(3,5-di Cl)	S	240	53
11h	2-F	C_6H_5(4-NO_2)	S	264	57

[a] Calculated from **3** and determined by HPLC chromatography detection at 254 nm for X = O, whereas the yields were calculated from **5** and isolated yield for X = S.

potassium carbonate at room temperature to give sulfide **12** in a quantitative yield. Disappearance of the peak for thiol proton (singlet at δ 12.42 ppm for **11c**) was concurrent with an appearance of the peaks for two methylene protons (two singlets at δ 3.74 and 4.12) and ethyl protons (quartet at δ 4.08 and triplet at δ 1.18 with $J = 7.2$ Hz) in the ^{1}H NMR spectrum, results of which were a coincidence with the structure **12**.

A successful result was obtained for the syntheses of **9** or **11** when a one-pot parallel synthetic reaction was carried out, starting from γ-aminoacetoacetanilide **3** and isocyanate or isothiocyanate derivative and followed by a treatment of *p*-TSA without isolation of intermediate **5** or **6**. Table 2 provides a list of prepared products with melting points and yields.

In conclusion, we synthesized new γ-aminoacetoacetanilide derivatives **3**, which proved to be versatile building blocks for the synthesis of heterocyclic compound libraries with molecular diversity. The γ-aminoacetoacetanilide derivatives **3**, were subjected to isocyanates or isothiocyanates followed by treatment with an acid catalyst (*p*-TSA) to afford the corresponding 1,3-imidazolin-3-ones **9** or mercaptoimidazole **11** good to moderate yields.

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Supporting Information Available. Experimental details; characterization data, and ^{1}H and ^{13}C NMR, ^{1}H−^{1}H COSY, NOESY, HMBC, and HMQC spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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