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# Triethylamin-Mediated Addition of 2-aminoethanethiol Hydrochloride to Chalcones: Synthesis of 3-(2-aminoethylthio)-1-(Aryl)-3-(Thiophen-2-yl) Propan-1-ones and 5,7-diaryl-2,3,6,7-tetrahydro-1,4-thiazepines

**Meliha Burcu Gürdere, Ali Cemal Emeç, Osman Nuri Aslan, Yakup Budak & Mustafa Ceylan**

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# Triethylamin-Mediated Addition of 2-Aminoethanethiol hydrochloride to Chalcones: Synthesis of 3-(2-Aminoethylthio)-1-(aryl)-3-(thiophen-2-yl) propan-1-ones and 5,7-Diaryl-2,3,6,7-tetrahydro-1,4-thiazepines

Meliha Burcu Gürdere[1,], Ali Cemal Emeç[1], Osman Nuri Aslan[1], Yakup Budak[1], Mustafa Ceylan[1]

[1]Department of Chemistry, Faculty of Arts and Sciences, Gaziosmanpasa University, Tokat, Turkey

Corresponding author, E-mail: burcu.gurdere@gop.edu.tr

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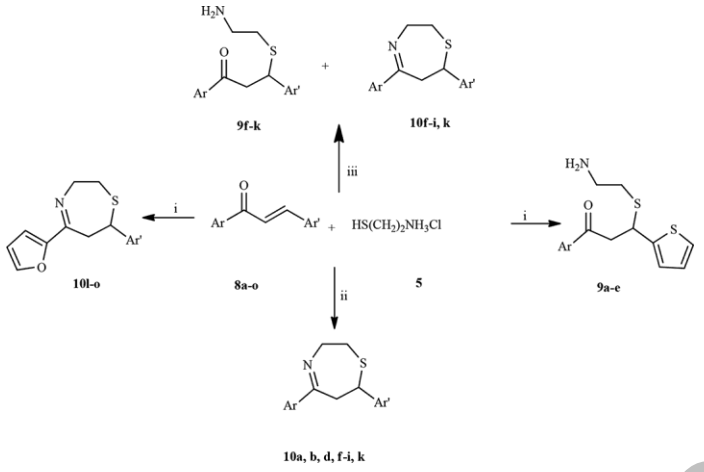
## Abstract

The triethylamin-mediated addition of 2-aminoethanethiol hydrochloride to chalcone analogues was investigated. This addition - bearing a 2-thienyl group at the 3-position gave the only addition adduct at room temperature for 3 hours, whereas the chalcones bearing the 2-furyl group at the 1-position gave an addition-cyclization product (1, 4-thiazepine) in the same conditions. The effect of the groups to the reaction was investigated by changing the 1- and 3-position groups. The chalcones bearing the 2-thienyl group at the 1-position and the others afforded the mixture of products in different ratio at r.t. for 0.5-24 hours. Moreover, the addition-cyclization products (1, 4-thiazepine) were obtained under reflux conditions for 36 hours. The structures of the synthesized compounds were elucidated by $^{1}$H NMR, $^{13}$C NMR, IR, and the elemental analysis.




**KEYWORDS:** 1,4-thiazephines, Chalcones, Triethylamin, 2-aminoethanethiol hydrochloride

## 1. INTRODUCTION

1, 4-Thiazepinones and 1, 4-thiazepines are important compounds whose biological and pharmacological properties have received much attention.[1,2] 1,4-Thiazepinones derivatives such as 1,4-thiazepin-5-one[3,4] and -2,4-dione[5] have been developed for the treatment of cancer, heart and inflammatory diseases. Most of these derivatives act as an enzyme inhibitor.[6-8] For the synthesis of these compounds, there have been are various methods developed such as addition,[9] condensation,[10] coupling[11,12] and rearrangement.[13] For example, some 1,4-thiazepin-5-ones have been obtained from the ring expansion of acetylenic thiazoles.[3] Highly functionalized 2,3,4,7-tetrahydro[1,4]thiazepines have been synthesized from the addition-condensation of sodium 2,2-dicyanoethene-1,1-bis(thiolate) to 2-chloroethylamine hydrochloride in water[6] and from thiazolidines and □-enaminonitriles.[1] However, 5,7-disubstituted-2,3,6,7-[1,4] thiazepine derivatives have generally been synthesized by the thia-Michael addition of 2-aminoethanethiol to □,□-



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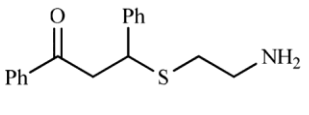
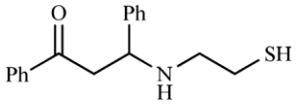
unsaturated carbonyls.[14] According to our knowledge, a few studies have reported on the relationship to the thia-Michael addition of 2-aminoethanethiol (**1**) to chalcone.[15,16] It has also previously been reported that the reaction of 2-aminoethanethiol (**1**) with chalcone in benzene gives a mixture of two mono-adducts (**2** and **3**) or a bisadduct (1,4-thiazepine) (**4**), depending on the molar ratios used.[17] Recently, Kodomari et al. have reported[18] that when the reaction was carried out in the presence of silica-gel under solvent-free condition, the a cyclization product (1,4-thiazepine) (**4**), was obtained as a sole product, but only one example was reported.




**2**

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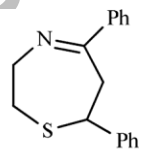


**4**

In this paper, we revisited the thia-Michael addition of 2-aminoethanethiol hydrochloride (**5**) to chalcones. The triethylamin-mediated addition of 2-aminoethanethiol hydrochloride (**5**) to particular chalcones bearing 2-thienyl and 2-furyl groups at the 1- and/or 3-position and synthesis of the novel mono adduct products (3-(2-Aminoethylthio)-1-(aryl)-3-(thiophen-2-yl)propan-1-ones) (**9a-o**) and the novel (5,7-diaryl-2,3,6,7-tetrahydro-1,4-thiazepines) (**10a-o**) are reported.

## 2. RESULTS AND DISCUSSION

The starting compounds (chalcone analogues) (**8a-o**) were obtained by base-catalyzed condensation of the appropriately substituted acetophenone, 2-furyl methyl ketone and 2-thienyl methyl ketone with substituted benzaldehydes, furfural, and thiophene-2-



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carbaldehyde in the presence of NaOH in EtOH at room temperature in yields of 82–98%.[19] The structures of all the synthesized chalcone derivatives were assigned on the basis of spectroscopic (IR, $^{1}$H-, $^{13}$C-NMR and elemental analysis) data, and comparison with their authentic sample.[20,21]

In the second stage of study, the in thia-Michael additions (1,4-addition) of 2-aminoethanethiol hydrochloride (**5**) to chalcone analogues (**8a-o**) was investigated. The reaction between chalcone (**8a**) and 2-aminoethanethiol hydrochloride (**5**) was chosen as the model reaction (Scheme 2) in order to determine optimum conditions. The results are summarized in Table 1. When the reaction was performed in the solvent (such as $CH_3OH$, THF, DMSO and $CH_2Cl_2$) without catalyst (entries 1-6, Table 1), and aqueous NaOH (as a catalyst) in $CH_3OH$ (entry 7, Table 1), the addition failed. In the case of $CH_2Cl_2$ aqueous NaOH or KOH and $CH_2Cl_2$, $I_2$, TEA (triethylamine) at r.t for 3h. and/or $CH_2Cl_2$, $I_2$, TEA under the reflux condition for 3h, the addition product, 3-(2-aminoethylthio)-1-(4-methoxyphenyl)-3-(thiophen-2-yl)propan-1-one (**9a**), was occurred but chalcone (**8a**) was unconsumed and the product rates determined from the $^{1}$H NMR spectrum was given in Table 1 (entries 8-12). When the reaction was performed in $CH_2Cl_2$ in the presence of TEA at room temperature for 3 hours, the adduct **9a** was obtained as the sole product in yield of 91% (entry 13, Table 1). The reaction was continued for 24 hours at r.t.; and obtained the mixture of products at a ratio of 3:1 (entry 14, Tab. 1). The same reaction was repeated under reflux conditions for 3, 24 and 36 hours. The mixtures of products (**9a** and **10a**) were obtained at a ratio of 2.5:1 and 1:1.5 for 3 and 24 hours, respectively, (entry 15, 16, Tab. 1). Finally, refluxing for 36 hours



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afforded the only addition-cyclization product (*E*)-5-(4-methoxyphenyl)-7-(thiophen-2-yl)-2,3,6,7-tetrahydro-1, 4-thiazepine (**10a**) in a good yield (86%) (Entry 17, Tab.1).

After the optimized conditions, we continued with the reactions with the other chalcones (8**b-o**). The reaction of chalcones **8a-e**, bearing 2-thienyl group at the 3-position, with 2-aminoethanethiol hydrochloride (**5**) in the presence of TEA in $CH_2Cl_2$ at room temperature for 3 hours gave the only addition products, 3-(2-aminoethylthio)-1-(aryl)-3-(thiophen-2-yl)propan-1-one **9a-e**, (Scheme 3; entry 1-5, Table 2).

The reaction of the chalcones **8l-o**, bearing 2-furyl group at the 1-position, with **5** was surprising. The addition of **5** to chalcones **8l-o** in the same conditions gave the only cyclisation products, (*E*)-5-(aryl)-7-(thiophen-2-yl)-2,3,6,7-tetrahydro-1,4-thiazepine **10l-o**, (Scheme 3; entry 12-15, Table 2).

In order to investigate the effect of the groups to the reaction, the reactions were continued by changing the 1- and 3-position groups. Chalcones **8f-i** (bearing 2-thienyl group at the 1-position and phenyl, 4-MeOPh, 4-ClPh and 2-thienyl group at the 3-position, respectively) and chalcones **8j, k** (bearing 2-furyl and phenyl group both at the 1- and 3-position, respectively) were submitted to the reaction with 2-aminoethanethiol hydrochloride (**5**) in the presence of TEA in $CH_2Cl_2$ at room temperature. The reactions were monitored by TLC and NMR. After 0.5-3 hours, it was observed that the mixture of products (**9** and **10**) occurred approximately at a ratio of 7:1, respectively, and the obtained yields from the $^1$H NMR were given (Scheme 3, entry 6-11, Table 2) (entries 6-



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11). The reactions were stopped after 0.5-3 hours for separation of products (**9f-k**) from the mixture. The mixture was submitted on a silica gel column and eluting with *n*-hexane/$CH_2Cl_2$ (3:1). During chromatography, it is observed that the product 9 converted to starting chalcone by elimination of 2-aminoethanethiol, so some of the products **9f-k** could not be isolated as purely.

Then, the same reactions were repeated in the same conditions for 24 hours, and the mixture of products (**9** and **10**) occurred as an approximately ratio of 1:4, respectively, (Scheme 3, entry 6-11, Table 2).

Finally, the chalcones (**8a**, **b**, **8d**, **8f-i** and **8**k) were reacted with 2-aminoethanethiol hydrochloride (**5**) under reflux conditions for 36 hours to obtain the addition-cyclization products (1,4-thiazepines) (**10a**, **b**, **10d**, **10f-i**, and **10**k) (Scheme 3, entry 16-23, Table 2). After the reactions were completed, the addition-cyclization products (**10a**, **b**, **10d**, **10f-i** and **10**k) were obtained as a sole product in high yields (Scheme 3, entry 16-23, Table 2).

All the synthesized compounds, except for **9k** and **10k**, are novel as our literature surveys. The structures of all the synthesized compounds were determined on the basis of spectral and literature data. All the spectral data are in good agreement with the proposed structures.

After all these results, we observed that the addition of 2-aminoethanethiol to the thienyl group containing, particularly 1-position, chalcones gave the addition products at room



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temperature and the short reaction times. On the contrary, the furyl group containing chalcones gave the addition-cyclization products in the same conditions. This situation can be explained by the electronic interactions. For this, we calculated some parameters of the model compounds **A-D** as theoretically. The theoretical calculations (HyperChem 7.05 Semi-empirical (AM1), Molecular Mechanic (MM+)) showed that compounds **C** and **D** are more stable than compounds **A** and **B** (Table 3). According to the results, it can be said that the repulsion between sulfur atoms and/or sulphur and nitrogen atom is greater than the repulsion between oxygen atoms and/or oxygen and nitrogen atom. The strong repulsion in the molecules **A** and **B** are increased to the strain energy and the heat of formation of them. Thus cyclization cannot occur at room temperature and short reaction times.

## 3. CONCLUSIONS

In summary, the triethylamin-mediated addition of 2-aminoethanethiol hydrochloride (**5**) to chalcone analogues was investigated. The addition of 2-aminoethanethiol hydrochloride (**5**) to chalcones (**8a-e**) bearing 2-thienyl group at the 3-position gave the only addition adduct (**9a-e**) at room temperature for 3 hours, whereas the chalcones (**8l-o**) bearing 2-furyl group at the 1-position gave the addition-cyclization product (**10l-o**) (1, 4-thiazepine) in the same conditions. The effect of the groups to the reaction was investigated by changing the 1- and 3-position groups. The chalcones bearing 2-thienyl group at the 1-position, and the others, afforded the mixture of products a different ratio at r.t. for 0.5-24 hours. Further, the addition-cyclization products (1, 4-thiazepine) were obtained under reflux conditions for 36 hours.



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## 4. EXPERIMENTAL

All the chemicals and solvents employed in the synthesis were supplied by Merck (Germany) and Fluka (Germany) and used without purification. The melting points were measured on an Electrothermal 9100 apparatus. The IR spectrums (KBr disc or $CHCl_3$) were recorded on a Jasco FT/IR-430 spectrometer. The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance DPX-400 instrument. As internal standards served TMS ( 0.00) for $^1H$ NMR and $CDCl_3$ ( 77.0) for $^{13}C$ NMR spectroscopy *J* values are given in Hz. The multiplicities of the signals in the $^1H$ NMR spectra are abbreviated by s (singlet), d (doublet), t (triplet), q (quarted), m (multiplet), br (broad) and combinations thereof. The elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer.

### 4.1. General Procedure For The Synthesis Of 9a-E

The chalcone derivatives (1 equiv.) were dissolved in $CH_2Cl_2$ and stirred at room temperature for 5 min. To a stirred solution of chalcone were added to the solution of 2-aminoethanethiol hydrochloride (1.2 equiv.) and trimethylamine (1.2 equiv.) in 10 mL $CH_2Cl_2$ for a period of 15 min. The mixture was stirred at room temperature for 3 h. The progress of the reaction was followed by TLC. The reaction mixture was then diluted with water and extracted with $CH_2Cl_2$. Subsequently, the organic layer was dried over anhydrous sodium sulfate. The evaporating of the solvent under reduced pressure gave the corresponding solid products. The crude products were purified by recrystallization from *n*-hexane-$CH_2Cl_2$.

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**4.1.1. 3-(2-**Aminoethylthio**)-1-(4-Methoxyphenyl)-3-(Thiophen-2-Yl)Propan-1-One (9a)**

Yellow crystals, Yield (91%); mp: 106-108$^0$C. IR (KCl cm$^{-1}$): 3286, 3100, 2974, 2928, 2376, 1660, 1585, 1467, 1423, 1365, 1312, 1201, 1056, 1002, 965, 812, 715, 580. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 7.98 (d, *J* = 8.8 Hz, 2H, AA'), 7.42 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.13 (d, *J* = 3.6 Hz, 1H), 7,05 (d, *J* = 8.8 Hz, 2H, XX'), 6.93 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.85 (t, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 3.71 (dd, *J* = 17.2, 8.0 Hz, 1H, A), 3.60 (dd, *J* = 17.2, 6.4 Hz, 1H, B), 3.35 (s ,–$NH_2$), 2.95-2.85 (m, 2H), 2.75-2.65 (m, 2H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm): 195.2, 163.8, 146.5, 140.9, 130.9 (2C), 127.1, 126.4, 125.7, 114.4 (2C), 56.1, 45.2, 38.9, 28.4; 21.8. Anal. Cald for $C_{16}H_{19}NO_2S_2$: C, 59.78; H, 5.96; N, 4.36; S, 19.95. Found: C, 59.77; H, 5.74; N, 4.23; S, 19.89.

**4.2. General Procedure For The Synthesis Of 9f-K**

The chalcone derivatives (1 equiv.) were dissolved in $CH_2Cl_2$ and stirred at room temperature for 5 min. To a stirred solution of chalcone were added to the solution of 2-aminoethanethiol hydrochloride (1.2 equiv.) and trimethylamine (1.2 equiv.) in 10 mL $CH_2Cl_2$ for a period of 15 min. The mixture was stirred at room temperature for 0.5 or 3 h. The progress of the reaction was followed by TLC. After 0.5-3 hours, the reaction mixture was diluted with water and extracted with $CH_2Cl_2$. Subsequently, the organic layer was dried over anhydrous sodium sulfate. The evaporating of the solvent under reduced pressure gave the corresponding solid products. The crude products were subjected to on a silica gel column.

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**4.2.1. 3-((2-Aminoethyl)Thio)-3-Phenyl-1-(Thiophen-2-Yl)Propan-1-One (9f)**

Viscous oil, Yield (58%). IR (KCl $cm^{-1}$): 3075, 3026, 2929, 2843, 2030, 1652, 1617, 1540, 1517, 1490, 1450, 1433, 1414, 1352, 1330, 1278, 1232, 1217, 1182, 1065, 1044. $^{1}$H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (d, *J* = 3.6, 1H), 7.62 (d, *J* = 4.8 Hz, 1H), 7.43-7.41 (m, 2H), 7.34-7.29 (m, 2H), 7.23 (dd, *J* = 4.8, 3.6 Hz, 1H), 7.11-7.09 (m, 1H), 4.54 (t, *J* = 7.2 Hz, 1H), 3.55-3.39 (m, 2H), 2.82-2.71 (m, 2H), 2.51-2.39 (m, 2H), 1.32 (bs, 2H, $-NH_2$). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ (ppm): 186.8, 142.5, 130.2, 128.9, 128.5, 128.2, 128.1, 127.9, 127.8, 127.5, 127.1, 55.8, 42.0, 36.6, 29.5. Anal. Cald for $C_{15}H_{17}NOS_2$: C, 61.82; H, 5.88; N, 4.81; S, 22.01. Found: C, 61.76; H, 5.79; N, 4.69; S, 21.98.

**4.3. General Procedure For The Synthesis Of 10a, B, 10d, 10f-I And 10k:**

The chalcone derivatives (1 equiv.) were dissolved in $CH_2Cl_2$ and stirred at room temperature for 5 min. To a stirred solution of chalcone were added to the solution of 2-aminoethanethiol hydrochloride (1.2 equiv.) and trimethylamine (1.2 equiv.) in 10 mL $CH_2Cl_2$ for a period of 15 min. The mixture was stirred at reflux temperature for 36 h. The progress of the reaction was followed by TLC. The reaction mixture was then diluted with water and extracted with $CH_2Cl_2$. Subsequently, the organic layer was dried over anhydrous sodium sulfate. The evaporating of the solvent under reduced pressure gave the corresponding solid products. The crude products were purified by recrystallization from *n*-hexane-$CH_2Cl_2$.

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**4.3.1. 5-(4-Methoxyphenyl)-7-(Thiophen-2-Yl)-2,3,6,7-Tetrahydro-1,4-Thiazepine (10a)**

Colorless crystals, Yield (86%); mp: 154-157$^0$C. IR (KCl cm$^{-1}$): 3070, 2926, 2847, 2035, 1891, 1615, 1581, 1511, 1455, 1423, 1353, 1317, 1300, 1246, 1180, 1109, 1081, 1066, 1027. $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, *J* = 4.8 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H, AA'), 7.20 (d, *J* = 3.6 Hz, 1H),7.02 (dd, *J* = 4.8, 3.6 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H, XX'), 4.47 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.17-4.11 (dd, *J* = 12.6, 10.0 Hz, 1H), 3.95 (d, *J* = 10.4 Hz, 1H), 3.84 (s, 3H), 3.79-3.73 (dd, *J* = 14.4, 10.4 Hz, 1H), 3.56 (d, *J* = 14.0 Hz, 1H), 3.04-2.98 (dd, *J* = 14.8, 9.2 Hz, 1H), 2.72-2.67 (dd, *J* = 14.6, 6.4 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ (ppm): 166.1, 159.1, 146.8, 134.6, 130.2, 128.2 (2C), 127.7, 127.5, 114.2 (2C), 55.3, 54.5, 42.2, 41.3, 29.6. Anal. Cald for $C_{16}H_{17}NOS_2$: C, 63.33; H, 5.65; N, 4.62; S, 21.13. Found: C, 63.16; H, 5.58; N, 4.49; S, 21.08.

**4.4. General Procedure For The Synthesis Of 10l-O**

The chalcone derivatives (1 equiv.) were dissolved in $CH_2Cl_2$ and stirred at room temperature for 5 min. To a stirred solution of chalcone were added to the solution of 2-aminoethanethiol hydrochloride (1.2 equiv.) and trimethylamine (1.2 equiv.) in 10 mL $CH_2Cl_2$ for a period of 15 min. The mixture was stirred at room temperature for 3 h. The progress of the reaction was followed by TLC. The reaction mixture was then diluted with water and extracted with $CH_2Cl_2$. Subsequently, the organic layer was dried over anhydrous sodium sulfate. The evaporating of the solvent under reduced pressure gave the corresponding solid products. The crude products were purified by recrystallization from *n*-hexane-$CH_2Cl_2$.

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**4.4.1. (*E*)-5-(Furan-2-Yl)-7-(4-Methoxyphenyl)-2,3,6,7-Tetrahydro-1,4-Thiazepine (10l)**

Colorless crystals, Yield (98%); mp: 121-123 $^0$C. IR (KCl cm$^{-1}$): 3100, 3073, 2974, 2925, 2845, 1639, 1596, 1568, 1503, 1461, 1409, 1241, 1196, 1165, 1009, 819, 763, 491. $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 2H, AA'), 6.86 (d, *J* = 8.4 Hz, 2H, BB'), 6.68 (d, *J* = 3.6 Hz, 1H), 6.41 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.50 (dd, *J* = 12.4, 6.4 Hz, 1H), 4.12 (t, *J* = 12 Hz, 1H), 3.87 (d, *J* = 6.4 Hz, 1H), 3.74 (s, 3H, -$OCH_3$), 3.63 (t, *J* = 6.4 Hz, 1H), 3.39 (d, *J* = 14.0 Hz, 1H), 2.96 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.65 (dd, *J* = 14.0, 6.8 Hz, 1H). $^{13}$C-NMR (100 MHz, $CDCl_3$) δ (ppm): 161.8, 159.0, 153.2, 145.1, 134.5, 128.4 (2C), 118.8 (2C), 114.1, 111.7, 55.3, 55.2, 41.5, 41.4, 29.5. Anal. Cald for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87; S, 11.16. Found: C, 66.74; H, 5.88; N, 4.80; S, 11.08.

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## SUPPLEMENTAL MATERIAL

Experimental procedures, characterization data, and NMR spectra of all compounds for this article can be accessed on the publisher's website.

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**Table 1.** Optimization studies of reaction condition

| Entry | Chalcone (equiv.) | $HS(CH_2)_2HN_3Cl$ (equiv.) | Solvent, Catalyst | Temp. | Time (h) | Products 9a:10a:8a |
|---|---|---|---|---|---|---|
| 1 | 1 | 1 | $CH_3OH$ | r.t | 3 | - |
| 2 | 1 | 1 | $CH_3OH$ | r.t | 24 | - |
| 3 | 1 | 1 | $CH_3OH$ | ref. | 3 | - |
| 4 | 1 | 1 | DMSO | r.t | 3 | - |
| 5 | 1 | 1 | THF | r.t | 3 | - |
| 6 | 1 | 1 | $CH_2Cl_2$ | r.t | 3 | - |
| 7 | 1 | 1.2 | $CH_3OH$, NaOH | r.t | 12 | - |
| 8 | 1 | 1.2 | $CH_2Cl_2$, KOH | r.t | 3 | 3:0:1 |
| 9 | 1 | 2 | $CH_2Cl_2$, KOH | r.t | 3 | 2:0:1 |
| 10 | 1 | 2 | $CH_2Cl_2$, KOH | r.t | 24 | 1:0:1.5 |
| 11 | 1 | 1.2 | $CH_2Cl_2$, $I_2$,TEA | r.t | 3 | 3:0:1 |
| 12 | 1 | 1.2 | $CH_2Cl_2$, $I_2$,TEA | ref. | 3 | 2:0:1 |
| 13 | 1 | 1.2 | $CH_2Cl_2$, | r.t | 3 | **9a** (91%) |



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| | | | | | | |
|---|---|---|---|---|---|---|
| | | | TEA | | | |
| 14 | 1 | 1.2 | $CH_2Cl_2$, TEA | r.t | 24 | 3:1:0 |
| 15 | 1 | 1.2 | $CH_2Cl_2$, TEA | ref. | 3 | 2:1:0 |
| 16 | 1 | 1.2 | $CH_2Cl_2$, TEA | ref. | 24 | 1:1.5:0 |
| 17 | 1 | 1.2 | $CH_2Cl_2$, TEA | ref. | 36 | **10a** (86%) |

-Not reaction

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Table 2. Synthesized compounds **9** and **10**

| Entry | Chalcone | Ar | Ar' | Temp. | Time (h) | Product (yield) | |
|---|---|---|---|---|---|---|---|
| | | | | | | 9 | 10 |
| 1 | **8a** | 4-$CH_3OPh$ | 2-thienyl | r.t. | 3 | **9a** (91) | - |
| 2 | **8b** | 4-ClPh | 2-thienyl | r.t. | 3 | **9b** (89) | - |
| 3 | **8c** | 4-BrPh | 2-thienyl | r.t. | 3 | **9c** (82) | - |
| 4 | **8d** | 4-$CH_3$Ph | 2-thienyl | r.t. | 3 | **9d** (86) | - |
| 5 | **8e** | 4-HOPh | 2-thienyl | r.t. | 3 | **9e** (89) | - |
| 6 | **8f** | 2-thienyl | Ph | r.t. | 0.5-3 | **9f** (59) | **10f** (9) |
| | | | | | 24 | **9f** (15) | **10f** (60) |
| 7 | **8g** | 2-thienyl | 4-$CH_3OPh$ | r.t. | 0.5-3 | **9g** (63) | **10g** (9) |
| | | | | | 24 | **9g** (14) | **10g** (62) |
| 8 | **8h** | 2-thienyl | 4-ClPh | r.t. | 0.5-3 | **9h** (70) | **10h** (10) |
| | | | | | 24 | **9h** (16) | **10h** (64) |
| 9 | **8i** | 2-thienyl | 2-thienyl | r.t. | 0.5-3 | **9i** (60) | **10i** (8) |
| | | | | | 24 | **9i** (13) | **10i** (55) |
| 10 | **8j** | 2-furyl | 2-furyl | r.t. | 0.5-3 | **9j** (57) | **10j** (8) |
| | | | | | 24 | **9j** (12) | **10j** (54) |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11 | **8k** | Ph | Ph | r.t. | 0.5-3 | **9k** (74) | **10k** (11) |
| | | | | | 24 | **9k** (12) | **10k** (76) |
| 12 | **8l** | 2-furyl | 4-$CH_3OPh$ | r.t. | 3 | - | **10l** (98) |
| 13 | **8m** | 2-furyl | 4-ClPh | r.t. | 3 | - | **10m** (84) |
| 14 | **8n** | 2-furyl | 4-BrPh | r.t. | 3 | - | **10n** (89) |
| 15 | **8o** | 2-furyl | 4-$CH_3Ph$ | r.t. | 3 | - | **10o** (94) |
| 16 | **8a** | 4-$CH_3OPh$ | 2-thienyl | ref. | 36 | - | **10a** (86) |
| 17 | **8b** | 4-ClPh | 2-thienyl | ref. | 36 | - | **10b** (89) |
| 18 | **8d** | 4-$CH_3Ph$ | 2-thienyl | ref. | 36 | - | **10d** (93) |
| 19 | **8f** | 2-thienyl | Ph | ref. | 36 | - | **10f** (83) |
| 20 | **8g** | 2-thienyl | 4-$CH_3OPh$ | ref. | 36 | - | **10g** (94) |
| 21 | **8h** | 2-thienyl | 4-ClPh | ref. | 36 | - | **10h** (84) |
| 22 | **8i** | 2-thienyl | 2-thienyl | ref. | 36 | - | **10i** (85) |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 23 | **8k** | Ph | Ph | ref. | 36 | - | **10k** (95) |

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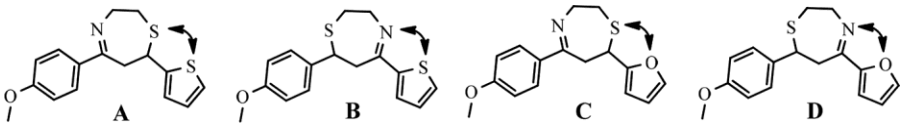
Table 3. The Calculated Total Energy (TE), Bonding Energy (BE), Heats of Formation ($H_f$) and Strain Energy (SE) for Compounds A, B, C and D




| Compd. | TE (kcal/mol) | BE (kcal/mol) | $H_f$ (kcal/mol) | SE (kcal/mol) |
|---|---|---|---|---|
| A | -73732.88 | -3886.83 | 38.69 | 29.98 |
| B | -73731.74 | -3885.74 | 39.59 | 29.29 |
| C | -76617.15 | -3903.86 | 15.63 | 25.45 |
| D | -76616.64 | -3902.35 | 16.14 | 24.30 |

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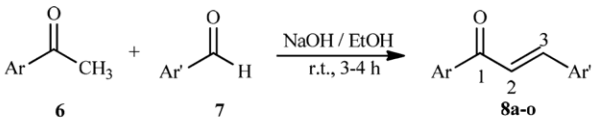
Scheme 1. Synthesis of chalcone analogues




**6** **7** **8a-o**

**8a**) Ar = 4-$CH_3$OPh, Ar' = 2-thienyl; **8b**) 4-ClPh, Ar' = 2-thienyl; **8c**) Ar = 4-BrPh, Ar' = 2-thienyl;

**8d**) Ar = 4-$CH_3$Ph, Ar' = 2-thienyl; **8e**) Ar = 4-HOPh, Ar' = 2-thienyl; **8f**) Ar = 2-thienyl, Ar' = Ph;

**8g**) Ar = 2-thienyl, Ar' = 4-$CH_3$OPh; **8h**) Ar = 2-thienyl, Ar' = 2-thienyl; **8i**) Ar = 2-furyl, Ar' = 2-furyl;

**8j**) Ar = Ph Ar' = Ph; **8k**) Ar = 2-furyl, Ar' = 4-$CH_3$OPh; **8l**) Ar = 2-furyl, Ar' = 4-ClPh;

**8m**) Ar = 2-furyl, Ar' = 4-BrPh; **8n**) Ar = 2-furyl, Ar' = 4-$CH_3$Ph; **8o**) Ar = 2-furyl, Ar' = 2-thienyl;

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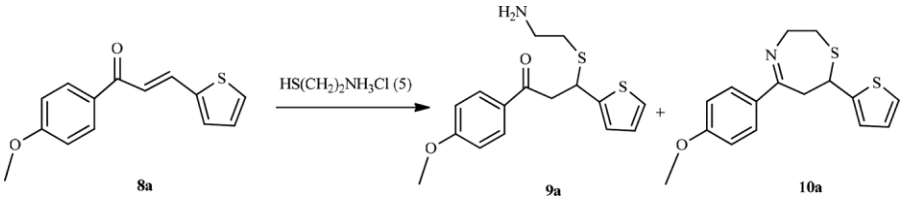
Scheme 2. Reaction of chalcone (**8a**) with 2-aminoethanethiol hydrochloride (**5**)

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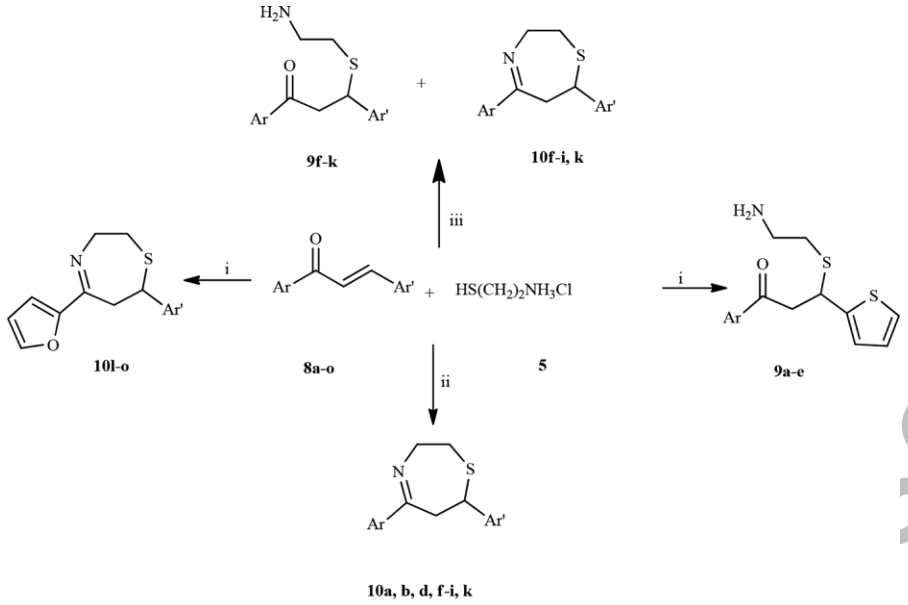
Scheme 3. Synthetic routes of compounds **9a-o** and **10a-o**




**Conditions: i)** $Et_3N$, $CH_2Cl_2$, room temp, 3 h; **ii**) $Et_3N$, $CH_2Cl_2$, reflux, 36 h.;

**iii**) $Et_3N$, $CH_2Cl_2$, room temp, 30 min. to 24 h.

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