Antiselective Three-Component Mannich Reactions in Thiopyran-4-one System

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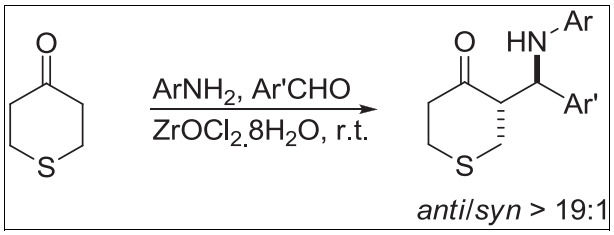

The one-pot, three-component Mannich reactions of thiopyran-4-one **1** with different aromatic aldehydes and aniline derivatives in the presence of catalytic quantities of $ZrOCl_2.8H_2O$ (15 mol %) led to rapid and high yield formation of various 3-methylamino substituted derivatives of **1** at room temperature. Spectroscopic and X-ray analyses of the products suggested the formation of the anti stereoisomers as the major product of the reactions.

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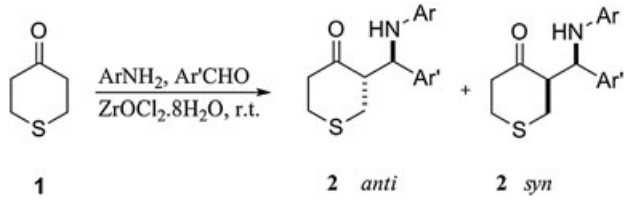
INTRODUCTION

Thiopyran structures constitute as one of the most important classes of sulfur containing heterocycles because of their usefulness in accessing certain natural and unnatural products [1–4]. In addition, there is a possibility to remove the sulfur atom of the thiopyran unit at the final stage of multistep syntheses. This provides the opportunity to access the target structures which are not easily prepared by direct standard procedures [5, 6]. This strategy was successfully demonstrated by Ward *et al*. in the Diels–Alder reactions of thiopyran dienes as useful surrogates for unreactive terminally *cis* substituted dienes [7, 8] and in tandem aldol reactions of thiopyranones to access polypropionate building blocks [9–11].

Today, multicomponent reactions (MCR's) are of very prominent position in synthetic organic chemistry since they facilitate combination of three or more components in one step allowing one-pot access to complex target products and libraries of desired molecules [12–15]. In this concept, the one-pot aminoalkylation of carbonyl compounds bearing α acidic protons, known as Mannich reaction [16], is one of the most widely studied MCRs [17–19]. The reaction provides direct access to β-amino carbonyl compounds which are found as the key substructure of many natural products [20], possess a wide array of biological activities [21], and are key versatile intermediates in synthetic organic chemistry [22–25]. Many one-pot procedures are offered in recent years to widen the synthetic scope of the Mannich reaction by using asymmetric catalysis [26–31], aqueous conditioned reactions [32–38], high pressure induced by water-freezing [39], rare earth metal containing catalysts [40, 41], Lewis acids [42–44], and silyl enol ethers [45].

Recently Hashemi's group reported an anti stereoselective synthesis of β-amino ketones *via* direct Mannich reactions of cyclic ketones catalyzed by $ZrOCl_2{\cdot}8H_2O$ [46], where reactions completed in relatively very short time periods. Base on this report, we were persuaded to apply the results to those heterocyclic systems which have been under our investigations in recent years [47–51]. Thiopyran-4-one **1** was chosen as an appropriate probe to evaluate this idea. A search in the literature revealed two related recent communications on Mannich reactions in thiopyran systems. The first one presnted only a single example of Mannich reactions [52] of **1** while the second one included several related examples [53]. However, both procedures took one to two days to complete and did not proceed at room-tenperature. In this work, we report the one-pot three-component combination of **1** with aromatic aldehydes and aniline derivatives leading to high yield formation of the respective β-amino thiopyran-4-ones in less than one hour time periods (Scheme 1).

Scheme 1



RESULTS AND DISCUSSION

We first optimized the reaction of **1** with 4-methylbenzaldehyde and aniline by using various sets of conditions. Experiments showed that the best results would be obtained in ethanolic mixture of the reactants and down to 15 mol % of $ZrOCl_2 \cdot 8H_2O$ would be enough to complete the process. Table 1 highlights the results obtained from the one-pot combination of **1** with aniline and various aromatic aldehydes at room temperature. Under the optimized conditions, reaction of **1** with 4-methylbenzaldehyde and aniline led to complete disappearance of the starting materials and formation of 83% of a single product within half an hour. Analysis of the ^{1}H NMR spectrum of the reaction mixture showed the presence of the respective β-amino heterocyclic ketone **2a** as the major compound in the mixture (Entry 1). The stereochemistry of the product was assigned as anti [46, 52, 53]. To confirm the stereochemistry of the product, a single crystal of **2a** was obtained from ethyl acetate and subjected to X-ray crystallographic analysis. The results, depicted in Figure 1, clearly illustrate the formation of the **2a** with anti configuration.

Under the conditions, 4-methoxybenzaldehyde behaved in the same manner to give anti product **2b** in 80% yield within 20 min (entry 2). Other aromatic (entry 3–5) or heteroaromatic aldehydes (entries 6–7) all gave their respective products in short time periods. In all cases, rapid completion of the reactions and formation of a major product in relatively high yields was observed. To further show the generality of the method, the reactions of **1** with various aromatic aldehydes and substituted anilines were evaluated next using the above conditions. Consequently, the respective β-amino adducts of **1** with anti stereochemistry were obtained in high yields over short reaction time periods (entries 8–14).

On the basis of the observed results, a mechanistic pathway could be suggested via which $ZrOCl_2$ is constantly recycled throughout the reaction to catalyze the addition of the enolate of **1** to the immine moiety derived from the condensation of the reacting aldehyde with aniline (Fig. 2).

CONCLUSIONS

In summary, we have disclosed a general and efficient three-component method for room-tempearture Mannich reactions of thioyran-4-one system leading to formation of the respective β-amino products. Reactions are fast, conditions are mild, and anti products are obtained selectively from the reaction mixtures by recrystallization of the solid precipitate. Application of the results to other heterocyclic systems is currently under investigation in our laboratories.

EXPERIMENTAL

General. Melting points are uncorrected. IR spectra were recorded on a Bruker Vector-22 infrared spectrometer. NMR spectra were obtained on a FT-NMR Bruker UltraShield™ (500 MHz) as $CDCl_3$ or DMSO-d_6 solutions using TMS as internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. Mass spectra were obtained on a Fisons 8000 Trio instrument at ionization potential of 70 ev. Thiopyran **1** was prepared according to a known method [54]. Other chemicals were purchased from commercial sources and purified prior to use, where necessary.

Typical procedure. To a solution of aniline (90 μL, 1 mmol) in EtOH (2 mL), were added *p*-methylbenzaldehyde (118 μL, 1 mmol), **1** (116 mg, 1 mmol), and $ZrOCl_2.8H_2O$ (48 mg, 15 mol %) successively at room temperature and the mixture was stirred at the same temperature for 30 minutes. After completion of the reaction, ethyl acetate (15 mL) was added and the mixture was washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was recrystallized from EtOAc to afford 259 mg (83%) of anti **2a**.

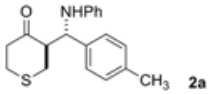
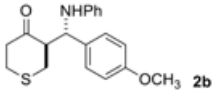
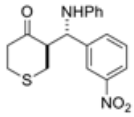
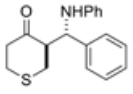
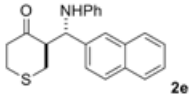
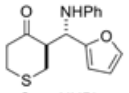
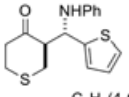
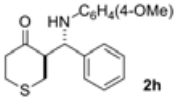
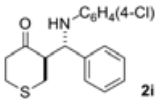
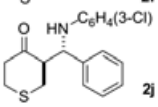
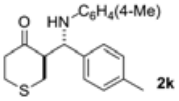
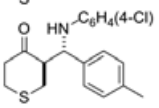
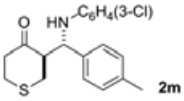
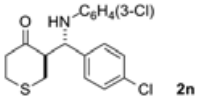
3-((Phenylamino)(p-tolyl)methyl)dihydro-2H-thiopyran-4(3H)-one (2a). Mp: 110–112°C; IR (KBr): 3334, 1703, 1600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.65-2.71 (m, 2H), 2.87-2.93 (m, 2H), 2.97-3.04 (m, 3H), 4.45 (br s, 1 H), 5.24 (d, *J*=9.5 Hz, 1H), 6.63 (d, *J*=8 Hz, 2H), 6.69 (t, *J*=7.5 Hz, 1H), 7.12 (dd, *J*=7.7, 8 Hz, 2H), 7.18 (d, *J*=7.7 Hz, 2H), 7.34 (d, *J*=7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5, 31.5, 33.9, 42.7, 57.1, 59.5, 114.3, 118.4, 127.5, 129.5, 130.0, 137.9, 146.9, 210.5; MS (70 eV): m/z 311 (M^+), 195, 104; Anal. Calcd. for $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50. Found: C, 73.08; H, 6.75; N, 4.44.

3-((4-Methoxyphenyl)(phenylamino)methyl)dihydro-2H-thiopyran-4(3H)-one (2b). Mp: 158–160°C; IR (KBr): 3334, 1703, 1600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.67-2.70 (m, 2H), 2.87-2.93 (m, 2H), 2.98-3.04 (m, 3H), 4.50 (br s, 1 H), 5.26 (d, *J*=9.5 Hz, 1H), 6.64 (d, *J*=8 Hz, 2H), 6.70 (t, *J*=7.5 Hz, 1H), 7.13 (dd, *J*=7.5, 7.8 Hz, 2H), 7.19 (d, *J*=7.5 Hz, 2H), 7.36 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 31.5, 33.8, 42.7, 57.1, 59.5, 114.3, 118.4, 127.5, 129.5, 130.0, 137.8, 137.9, 147.0, 210.5; MS (70 eV): m/z 327 (M^+), 312, 196, 115; Anal. Calcd. for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28. Found: C, 70.09; H, 6.71; N, 4.35.

3-((3-Nitrophenyl)(phenylamino)methyl)dihydro-2H-thiopyran-4(3H)-one (2c). Mp:202–204°C; IR (KBr): 3356, 1699, 1600 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66-2.71 (m, 2H), 2.79-2.84 (m, 1H), 2.97-3.02 (m, 4H), 4.61 (br s, 1H), 5.23 (d, *J*=7.7 Hz, 1 H), 6.55 (d, *J*=7.7 Hz, 2H), 6.69 (t, *J*=7.5 Hz, 1H), 7.10 (dd, *J*=7.5, 8 Hz, 2H), 7.50 (t, *J*=7.5, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 8.11 (dd, *J*=1.5, 8 Hz, 1H), 8.29 (dd, *J*=1.5, 2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.4, 34.0, 43.3, 57.2, 59.1, 114.1, 119.1, 122.5, 123.3, 129.8, 130.2, 133.9, 143.7, 146.2, 149.2, 209.4; MS (70 eV) m/z (%), 342 (M^+), 227, 181, 115; Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.88; H, 5.17; N, 7.91.

Table 1

One-pot $ZrOCl_2.8H_2O$ catalyzed Mannich reactions of **1**.

Entry	Reactants	Product	Time (Min)	Yield (%)[a]
1	4-methylbenzaldehyde + aniline	 **2a**	30	83
2	4-methoxybenzaldehyde + aniline	 **2b**	20	80
3	3-nitrobenzaldehyde + aniline	 **2c**	18	89
4	Benzaldehyde + aniline	 **2d**	27	95
5	2-naphthaldehyde + aniline	 **2e**	15	88
6	Furfural + aniline	 **2f**	25	82
7	thienyl aldehyde + aniline	 **2g**	27	78
8	Benzaldehyde + 4-methoxyaniline	 **2h**	22	85
9	Benzaldehyde + 4-chloroaniline	 **2i**	28	79
10	Benzaldehyde + 3-chloroaniline	 **2j**	25	82
11	4-methylbenzaldehyde + 4-methylaniline	 **2k**	25	82
12	4-methylbenzaldehyde + 4-chloroaniline	 **2l**	35	90
13	4-methylbenzaldehyde + 3-chloroaniline	 **2m**	30	75
14	4-chlorobenzaldehyde + 3-chloroaniline	 **2n**	20	80

[a]Isolated yields.

3-(Phenyl(phenylamino)methyl)dihydro-2H-thiopyran-4(3H)-one (2d). Mp: 214–216°C; IR (KBr): 3332, 1699, 1598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.47-2.53 (m, 1H), 2.55-2.56 (m, 1H), 2.74-2.90 (m, 5H), 4.61 (br s, 1H), 5.12 (d, *J*=9 Hz, 1H), 6.49 (d, *J*=8 Hz, 2H), 6.53 (t, *J*=7.5 Hz, 1H), 6.96 (dd, J=7.7, 8 Hz, 2H), 7.14 (t, *J*=7.5 Hz, 1H), 7.23 (dd, *J*=7.5, 7.7 Hz, 2H), 7.32 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.4, 33.7, 40.9, 56.6, 58.7, 114.1, 117.2, 128.1, 128.4, 129.3, 129.6, 142.1, 148.5, 209.4; MS (70 eV): m/z 297 (M^+), 208, 182, 115; Anal. Calcd. for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 72.34; H, 6.36; N, 4.63.

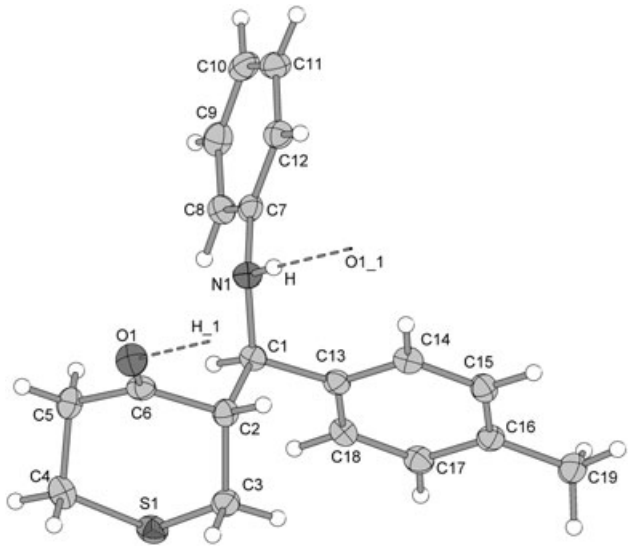


Figure 1. Crystal structure of **2a**. Displacement of ellipsoids at 50% probability level.

3-(Naphthalen-2-yl(phenylamino)methyl)dihydro-2H-thiopyran-4(3H)-one (2e). Mp: 120–122°C; IR (KBr): 3334, 1697, 1598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.66-2.70 (m, 1H), 2.71-2.74 (m, 1H), 2.91-2.95 (m, 2H), 2.98-3.08 (m, 3H), 4.61 (br s, 1H), 5.46 (d, *J*=9.5 Hz, 1H), 6.68-6.71 (m, 3H), 7.12 (dd, *J*=7.5, 8 Hz, 2H), 7.50-7.59 (m, 3H), 7.85-7.90 (m, 3H), 7.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.4, 33.9, 42.7, 57.6, 59.3, 114.3, 118.6, 124.8, 126.5, 126.8, 127.2, 128.2, 128.4, 129.4, 129.6, 133.5, 133.7, 138.3, 146.8, 210.4; MS (70 eV): m/z, 347 (M^+), 232, 165, 104; Anal. Calcd. for $C_{22}H_{21}NOS$: C, 76.04; H, 6.09; N, 4.03. Found: C, 76.36; H, 6.09; N, 4.11.

3-(Furan-2-yl(phenylamino)methyl)dihydro-2H-thiopyran-4(3H)-one (2f). Mp: 154–156°C; IR (KBr): 3342, 1703, 1598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.64-2.68 (m, 1H), 2.71-2.81 (m, 2H), 2.93-2.97 (m, 3H), 3.18-3.22 (m, 1H), 4.20 (br s, AH), 5.31 (d, *J*=8.2 Hz, 1H), 6.26-6.28 (m, 2H), 6.66 (d, *J*=7.7 Hz, 2H), 6.73 (t, *J*=7.3 Hz, 1H), 7.14 (dd, *J*=7, 7.5 Hz, 2H), 7.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.3, 33.8, 43.2, 51.9, 56.5, 108.5, 110.7, 114.4, 119.0, 129.7, 142.5, 146.9, 153.2, 209.4; MS (70 eV): m/z 287 (M^+), 172, 107; Anal. Calcd. for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.92; H, 6.12; N, 4.91.

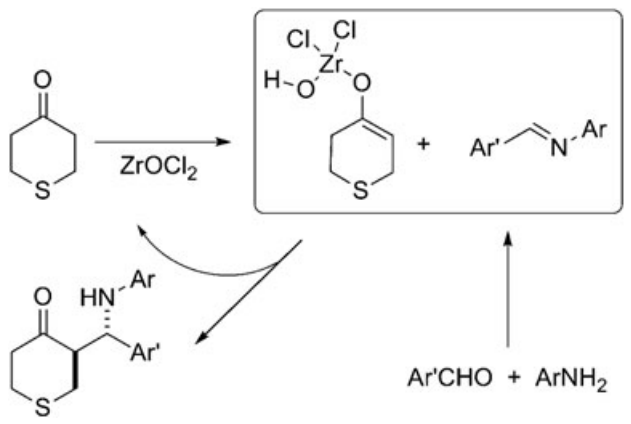


Figure 2. The proposed mechanistic pathway of the reaction.

3-((Phenylamino)(thiophen-2-yl)methyl)dihydro-2H-thiopyran-4(3H)-one (2g). Mp: 179–181°C; IR (KBr): 3325, 1701, 1597 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.65-2.68 (m, 1H), 2.77-2.81 (m, 2H), 2.94-3.02 (m, 4H), 4.32 (br s, 1H), 5.50 (d, *J*=8.2 Hz, 1H), 6.65 (d, *J*=8.0 Hz, 2H), 6.71 (t, *J*=7.3 Hz, 1H), 6.93 (dd, *J*=3.5, 4.5 Hz, 1H), 7.07 (d, *J*=3.5 Hz, 1H). 7.14 (dd, *J*=8, 7.5 Hz, 2H), 7.18 (d, *J*=5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4, 34.0, 43.0, 53.8, 59.6, 114.4, 119.0, 125.2, 126.1, 127.3, 129.6, 145.6, 146.7, 209.7; MS (70 eV): m/z 303 (M^+), 188, 123, 104; Anal. Calcd. for $C_{16}H_{17}NOS_2$: C, 63.33; H, 5.65; N, 4.62. Found: C, 62.93; H, 5.54; N, 4,81.

Methoxyphenylamino)(phenyl)methyl)dihydro-2H-thiopyran-4(3H)-one (2h). Mp: 149–151°C; IR (KBr): IR (KBr): 3331, 1699, 1597 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.65-2.67 (m, 1H), 2.67-2.70 (m, 1H), 2.88-2.92 (m, 3H), 2.95-3.00 (m, 2H), 3.71 (s, 3H), 4.30 (br s, 1H), 5.19 (d, *J*=9.5 Hz, 1H), 6.56 (d, *J*=9 Hz, 2H), 6.70 (d, *J*=9 Hz, 2H), 7.28 (t, *J*=7.5 Hz, 1H), 7.35 (t, *J*=7.5 Hz, 2H), 7.43 (d, J=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.5, 33.9, 42.6, 56.1, 58.2, 59.5, 115.2, 115.7, 127.6, 128.2, 129.2, 140.9, 141.1, 152.9, 210.4; MS (70 eV) m/z (%), 327 (M^+), 211, 196; Anal Calcd for $C_{19}H_{21}NO_2S$: C, 69.69; H, 6.46; N, 4.28. Found: C, 69.33; H, 6.12; N, 4.12.

Chlorophenylamino)(phenyl)methyl)dihydro-2H-thiopyran-4(3H)-one (2i). Mp: 170-172°C; IR (KBr): IR (KBr) 3367, 1695, 1595 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.66-2.72 (m, 2H), 2.85-2.93 (m, 2H), 2.98-3.03 (m, 3H), 4.53 (br s, 1H), 5.17 (d, *J*=9 Hz, 1H), 6.54 (d, *J*=9 Hz, 2H), 7.06 (d, *J*=9 Hz, 2H), 7.29 (t, *J*=7 Hz, 1H), 7.35 (dd, *J*=7, 7.5 Hz, 2H), 7.42 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 31.4, 33.7, 43.2, 56.7, 58.6, 115.5, 120.5, 128.2, 128.3, 129.3, 129.4, 141.7, 147.4, 209.3; MS (70 eV) m/z (%), 331 (M^+), 216, 138; Anal Calcd. for $C_{18}H_{18}ClNOS$: C, 65.15; H, 5.47; N, 4.22. Found: C, 65.34, H, 5.52; N, 4.18.

Chlorophenylamino)(phenyl)methyl)dihydro-2H-thiopyran-4(3H)-one (2j). Mp: 153–155°C; IR (KBr): IR (KBr) 3329, 1699, 1595 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.63-2.67 (m, 2H), 2.80-2.82 (m, 1H), 2.88-2.92 (m, 2H), 2.94-2.99 (m, 2H), 4.59 (br s, 1H), 5.13-5.15 (d, *J*=9 Hz, 1H), 6.42-6.44 (dd, *J*=2, 8 Hz, 1H), 6.55 (dd, *J*=1.5, 2 Hz, 1H), 6.61 (dd, *J*=1.5, 8 Hz, 1H), 6.96 (dd, *J*=2, 8 Hz, 1H), 7.25 (t, *J*=7 Hz, 1H), 7.34 (dd, *J*=7.5, 8 Hz, 2H), 7.40 (d, *J*=7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4, 33.8, 42.8, 57.4, 59.3, 112.4, 114.0, 118.4, 127.5, 128.4, 129.4, 130.5, 135.3, 140.4, 148.1, 210.3; MS (70 eV) m/z (%), 331 (M^+), 238, 216; Anal. Calcd. for $C_{18}H_{18}ClNOS$: C, 65.15; H, 5.47; N, 4.22. Found: C, 65.30; H, 5.43; N, 4.31.

(4-Methylphenyl)(p-tolylamino)methyl)dihydro-2H-thiopyran-4(3H)-one (2k). Mp: 155–157°C; IR (KBr): IR (KBr) 3342, 1707, 1618 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.35 (s, 3H), 2.64-2.70 (m, 2H), 2.87-2.93 (m, 2H), 2.97-3.04 (m, 3H), 4.33 (br s, 1H), 5.24 (d, *J*=9.5 Hz, 1H) 6.55 (d, *J*=8.5 Hz, 2H), 6.94 (d, *J*=8.5 Hz, 2H), 7.18 (d, *J*=8 Hz, 2H) 7.33 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 21.5, 31.5, 33.9, 42.6, 57.3, 59.5, 114.4, 127.5, 127.6, 129.9, 130.1, 137.8, 138.0, 144.6, 210.5; MS (70 eV) m/z (%), 325 (M^+), 210, 115; Anal. Calcd. for $C_{20}H_{23}NOS$: C, 73.81; H, 7.12; N, 4.30. Found: C, 73.98; H, 7.17; N, 4.46.

(4-Chlorophenylamino)(p-tolyl)methyl)dihydro-2H-thiopyran-4(3H)-one (2l). Mp: 169–171°C; IR (KBr): 3346, 1705, 1595 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.55-2.59

(m, 1H), 2.61-2.65 (m, 1H), 2.78-2.86 (m, 2H), 2.85-2.93 (m, 3H), 4.58 (d, *J*=8 Hz, 1H), 5.09 (dd, *J*=8, 8.5 Hz, 1H), 6.48 (d, *J*=8.5 Hz, 2H), 6.97 (d, *J*=8.5 Hz, 2H), 7.10 (d, *J*=8 Hz, 2H), 7.26 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 31.4, 33.8, 42.7, 57.2, 59.3, 115.3, 122.8, 127.5, 129.3, 130.0, 137.4, 138.0, 145.6, 210.3; Anal. Calcd. for $C_{19}H_{20}ClNOS$: C, 65.98; H, 5.83; N, 4.05 Found: C, 65.66; H, 5.58; N, 3.88.

(3-Chlorophenylamino)(p-tolyl)methyl)dihydro-2H-thiopyran-4 (3H)-one (2m). Mp: 151–153°C; IR (KBr): IR (KBr) 3346, 1705, 1595 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.64-2.68 (m, 1H), 2.68-2.71 (m, 1H), 2.84-2.86 (m, 1H), 2.87-2.91 (m, 1H), 2.95-2.99 (m, 1H), 3.01-3.03 (m, 2H), 4.57 (br s, 1H), 5.15 (d, *J*=9.5 Hz, 1H), 6.48 (dd, *J*=2, 8 Hz, 1H), 6.59 (dd, *J*=1.5, 2 Hz, 1H), 6.64 (dd, *J*=1.5, 7 Hz, 1H), 7.00 (t, *J*=8 Hz 1H), 7.18 (d, *J*=8 Hz, 2H), 7.31 (d, *J*=8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 31.4, 33.8, 42.8, 57.1, 59.3, 112.4, 114.0, 118.3, 127.4, 130.1, 130.5, 135.2, 137.3, 138.1, 148.1, 210.4; MS (70 eV) m/z (%), 345 (M^+), 230, 138; Anal. Calcd. for $C_{19}H_{20}ClNOS$: C, 65.98; H, 5.83; N, 4.05 Found: C, 65.66; H, 5.58; N, 3.88.

(4-Chlorophenyl)(3-chlorophenylamino)methyl)dihydro-2H-thiopyran-4(3H)-one (2n). Mp: 182–184°C; IR (KBr): IR (KBr) 3367, 1697, 1595 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65-2.68 (m, 1H), 2.69-2.74 (m, 1H), 2.82-2.86 (m, 1H), 2.91-2.94 (m, 1H), 2.96-3.04 (m, 3H), 4.67 (br s, 1H), 5.12 (d, *J*=9 Hz, 1H), 6.44 (dd, *J*=2, 8 Hz, 1H), 6.56 (dd, *J*=1.5, 2 Hz, 1H), 6.68 (dd, *J*=1.5, 7.8 Hz, 1H), 7.02 (t, *J*=8 Hz, 1H), 7.30 (d, *J*=8.5 Hz, 2H), 7.38 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.4, 33.8, 43.0, 57.0, 59.1, 112.4, 114.0, 118.7, 128.8, 129.6, 130.6, 134.2, 135.4, 138.9, 147.7, 209.9; MS (70 eV) m/z (%), 365 (M^+), 250, 137; Anal. Calcd. for $C_{18}H_{17}C_2NOS$: C, 59.02; H, 4.68; N, 3.82. Found: C, 58.87; H, 4.57; N, 3.74.

X-ray crystal structure analysis of 2a. Colorless crystal grown from ethyl acetate, data collection on an IPDS area detector system (Stoe) at 100 k, MoKα-radiation. $C_{19}H_{21}NOS$, M_r = 311.43, monoclinic, space group P $2_1/n$, Z = 4, a = 11.8541(5), b = 8.2037(3), c = 16.9561(8) Å, V = 1601.67(12) Å^3, d_c = 1.291 Mg/m^3, μ = 0.204 mm^{-1}. 11961 reflections to θ = 25.00°, 3393 independent, 2556 > 4σ(F), wR_2 = 0.0644 (all refl.), R = 0.0280 (for F>4σ(F)), Δρ (min/max) 0.239/–0.256 eÅ^{-3}. H-atoms localized and refined isotropically. Crystallographic data (excluding structure factors) for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-770540. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. Code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html

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