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A general synthesis of *N*-substituted 1,4-benzoxazine- and 1,4-benzothiazine-2-carboxylates via copper-catalyzed intramolecular amination of arylbromides

Ferdinand Melkonyan, Artiom Topolyan, Alexander Karchava *, Marina Yurovskaya

Department of Chemistry, Moscow State University, Moscow 119991, Russia

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ABSTRACT

Starting from *ortho*-bromosubstituted phenoxyacetates or (phenythio)acetates and primary amines, various *N*-substituted 4*H*-1,4-benzoxazine- and 4*H*-1,4-benzothiazine-2-carboxylates were synthesized in moderate to high yields by using a Cu(I)-catalyzed Ullmann-type cyclization as a key step. The method is simple to operate, tolerates many functional groups and does not require any additives.

1. Introduction

From the late 1900s, copper-catalyzed C–X bond-forming reactions have received considerable attention due to being both a compliment and an alternative to the methods employing palladium catalysts. The low cost, low toxicity and high stability of copper catalysts as well as simplicity of commonly used supporting ligands make the Cu-catalyzed cross-coupling reactions a superior chose in organic synthesis. A number of useful synthetic protocols have been developed for the synthesis of a wide range of organic compounds under mild conditions with use of an appropriate combination of copper source, base, ligand, and solvent.[1] In the addition to the above-mentioned advantages, in some specific cases, an application of a copper catalyst demonstrated a better result than palladium. These copper-catalyzed reactions have also been extensively applied in an intramolecular fashion in the assembly of a wide variety of heterocyclic compounds.[1,2]

Recently, we have successfully applied this methodology to the synthesis of *N*-alkyl and *N*-aryl substituted indole-3-carboxylates starting from *o*-bromophenylacetates by a three-step sequence of reactions involving: (i) α-formylation of *o*-bromophenylacetates, (ii) reaction of α-formylesters with primary amines, and (iii) Cu-catalyzed intramolecular cyclization *N*-substituted 3-amino-2-(2-bromophenyl)acrylates to indoles.[3] Our procedure is very simple to operate and can be performed under ligand-free conditions and an air atmosphere without loss of yield. In the continuation of our interest in exploring the intramolecular Ullmann reaction for the construction of heterocycles, we decided to apply the same synthetic sequence to (*o*-bromophenoxy)- and (*o*-bromophenylthio) acetates in an attempt to develop a new route to *N*-substituted 1,4-benzoxazines and 1,4-benzothiazines by using copper-catalyzed conditions in the absence of ligands and additives.

1,4-Benzoxazines[4] and 1,4-benzothiazines[5] ring systems are found in a broad range of natural and synthetic biologically active molecules. Among various biologically active compounds of these classes, 3-oxo[6] and 2,3-dihydro[7] derivatives have been studied extensively and several synthetic approaches to them have been proposed.[8–10] The synthesis and biological properties of the unsaturated derivatives have been much less documented. However, these templates also seem attractive for drug discovery programs. Some biologically active compounds of this class, including a natural product Cappamensin A, which possesses a promising anticancer activity[11] are depicted on Fig. 1.

The previously reported syntheses of unsaturated 1,4-benzoxazines and 1,4-benzothiazines are limited in number and mainly based on direct[17] or indirect[4,18] oxidation of the corresponding 2,3-dihydroderivatives, which in turn are usually available by multistep procedures.[7,8,10] All these approaches suffer from lengthy sequences, low overall yields, and, most of all, limited ability to vary substituents at the nitrogen.[4,8] Recently, several new

* Corresponding author. E-mail address: karchava@org.chem.msu.ru (A. Karchava).

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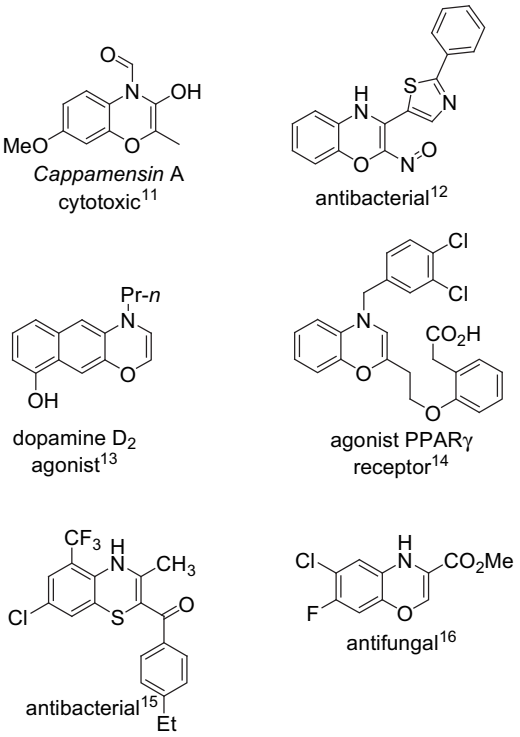


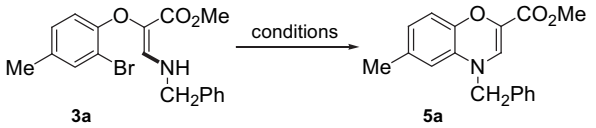
Fig. 1. Examples of biologically active unsaturated 1,4-benzoxazines and 1,4-benzothiazine.[11–16]

procedures using isocyanide chemistry[19] and a ring-closure metathesis strategy[20] have appeared. However, these methods were only developed for the preparation of *N*-unsubstituted derivatives. Herein, we describe a new general and straightforward approach to *N*-substituted 1,4-benzoxazine- and 1,4-benzothiazine derivatives by employing an intramolecular Ullmann-type N-arylation reaction as the key step for the assembly of a benzo-annelated six-membered heterocyclic core.[21]

2. Result and discussion

We began our research by preparing methyl 3-oxo-2-phenoxypropanoates **1a**–**d** and 3-oxo-2-phenylthiopropanoate (**2**). These compounds were obtained in high yields by formylation of the corresponding phenoxyacetates and phenylthioacetate with methyl formate (Scheme 1). Next, treatment of **1a** with equimolar amount of benzylamine in methanol and stirring the mixture for 8 h at ambient temperature afforded the enamines **3a** as a mixture of isomers in near quantitative yield and high purity (determined by GC/MS) after evaporation of methanol. The product **3a** was used as a model substrate to establish the optimal reaction conditions for the formation of the 4*H*-1,4-benzoxazine ring system via the copper-catalyzed Ullmann-type coupling/cyclization reaction (Table 1). We chose CuI as the catalyst source due to its low cost, air stability, and effectiveness in many cases. Optimizing the reaction conditions with regard to base, solvent, reaction temperature, and time revealed that the highest yield of methyl 4-benzyl-6-methyl-4*H*-1,4-benzoxazine-2-carboxylate (**5a**, 87%) and the total conversion of **3a** were obtained when the reaction was performed with 10 mol % CuI and 2 equiv of K_3PO_4 in DMF (1 M) at 110 °C for 16 h (Table 1, entry 4). Conducting the reaction at 85 °C (entry 1) led to a significant decrease in both yield of **5a** and conversion of **3a**; using 3 equiv of K_3PO_4 instead of 2 equiv at 85 °C did not improve the yield (entry 2). When Cs_2CO_3 (2 equiv) was used as the base the rate of the reaction increased substantially, and the comparable yield of **5a** (86%) as well as the quantitative conversion of **3a** were achieved after 6 h at 85 °C (entry 10), while K_2CO_3 as the base led to decreased yield (48%, entry 6). The effect of the catalyst loading was also investigated and experiments showed that the best results for this intramolecular coupling reaction were obtained with 10 mol % of CuI; the yield of **5a** was reduced with 5 mol % of the catalyst source (entry 9), and no reaction occurred in the absence of copper salt (entry 12). Finally, only a trace amount of the target product and recovery of the starting material were observed when toluene or 1,4-dioxane was used as the solvent (entries 7 and 8) and the cyclization did not proceed at all in methanol (entry 14). We also carried out an experiment with DMF as the sole solvent for the one-flask two-step preparation of **5a** from **1a** and benzylamine. The process was started by stirring of reagents in DMF at room temperature for 10 h (consumption of the starting materials was indicated by TLC), then 2 equiv of K_3PO_4 and 10 mol % CuI were added and the whole mixture was stirred at 110 °C for 16 h. The desired product was isolated in only 65% overall yield after column chromatography. Therefore, in the following investigation for the synthesis of *N*-substituted 1,4-benzoxazines and 1,4-benzothiazines we applied a 'single-flask' uninterrupted sequence of reactions[22] initiated in MeOH with subsequent removal of

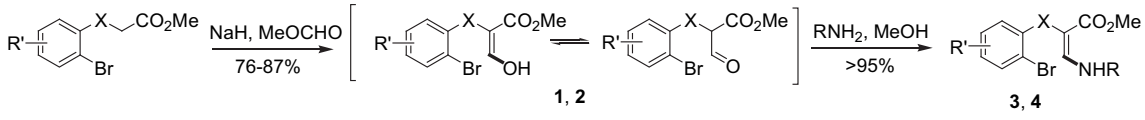
Table 1
Optimization of reaction conditions for the Cu-catalyzed cyclization of **3a** to **5a**[a]



3a **5a**

Entry	mol % of CuI	Base, equiv	Solvent	*T* (°C)	Time (h)	Yield[b], %
1	5	K_3PO_4, 2	DMF	85	20	40
2	5	K_3PO_4, 3	DMF	85	20	46
3	10	K_3PO_4, 2	DMF	85	20	49
4	**10**	**K_3PO_4, 2**	**DMF**	**110**	**16**	**87**
5	10	K_3PO_4, 3	DMF	110	16	72
6	10	K_2CO_3, 3	DMF	110	20	48
7	10	K_3PO_4, 2	Toluene	110	20	Trace
8	10	K_3PO_4, 2	1,4-Dioxane	110	20	Trace
9	5	Cs_2CO_3, 2	DMF	85	10	77
10	**10**	**Cs_2CO_3, 2**	**DMF**	**85**	**6**	**86**
11	10	Cs_2CO_3, 2	DMF	110	6	80
12	0	Cs_2CO_3, 2	DMF	110	20	0
13	10	K_3PO_4, 2	DMF	110	16	65[c]
14	10	K_3PO_4, 2	MeOH	65	20	0

Bold represents the most optimal reactions conditions for the synthesis.
[a] Reaction conditions: **3a** (3 mmol), base, CuI, solvent (3 mL) in sealed tube under an air atmosphere.
[b] Yield after chromatography on silica gel.
[c] DMF was used as the sole solvent for the preparation of **3a** and its subsequent cyclization to **5a**.



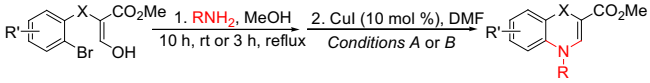
1, **3** X=O; R' = H (**a**); R' = 4-Me (**b**); R' = 4-CO_2Me (**c**); R' = 5-F (**d**). **2**, **4** X=S, R' = H

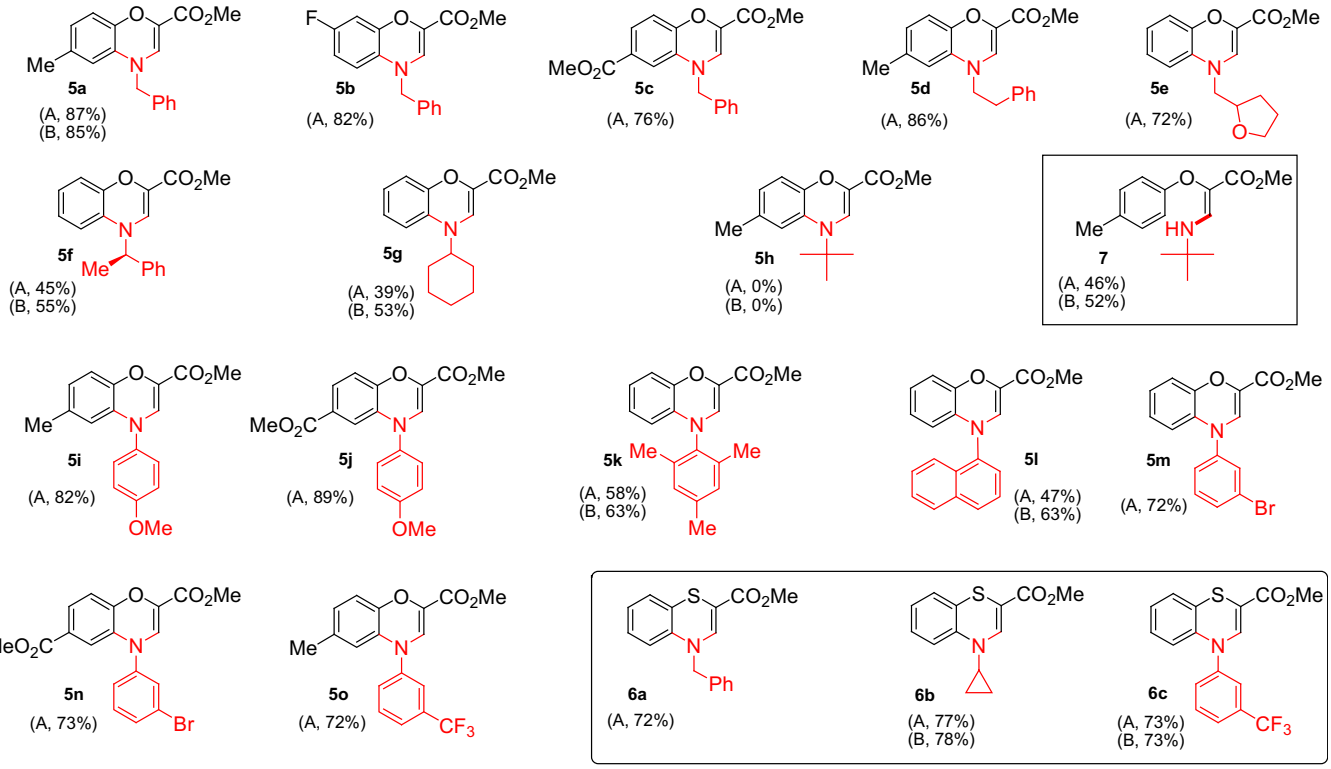
Scheme 1. Synthesis of formylesters **1**, **2** and enamines **3**, **4**.

volatile materials under reduced pressure and replacement of the solvent with DMF for the cyclization step.

With the optimized reaction conditions, we have explored the substrate scope and limitation. The results are summarized in Table 2. A series of diversified alkylamines and arylamines bearing different alkylamines (**5f** and **5g**) and *ortho*-substituted anilines (**5k** and **5l**) gave the corresponding products in low to moderate yields, although slightly higher yields were obtained when Cs_2CO_3 was employed as the base. Moreover, the reaction of *tert*-butylamine and **1b** was unproductive and resulted only in the formation of the debromination

Table 2
Synthesis of *N*-substituted 1,4-benzoxazines and 1,4-benzothiazines via a single-flask sequential procedure





Conditions A: K_3PO_4 (2 equiv), 110 °C, 16 h; *Conditions B*: Cs_2CO_3 2 (equiv), 85 °C, 6 h.

substitution patterns were employed to react with formylesters **1a**–**d** and **2** by stirring a solution of reagents in methanol for 10 h at room temperature (for alkylamines), or for 3 h at reflux (for anilines). In all cases the consumption of starting materials was confirmed by TLC analysis. All enamines **3** and **4** obtained after evaporation of methanol were used in the next step without further purification. In spite of the longer reaction time, we mainly used K_3PO_4 as the base due to its low cost (*conditions A*), but Cs_2CO_3 (*conditions B*) was also evaluated, especially in the cases of sterically hindered amines. Generally, our two-step sequence proceeded smoothly, affording the target 1,4-benzoxazines **5** and 1,4-benzothiazine **6** in moderate to good yields (Table 2). Very good yields of the products along with a quantitative conversion of starting materials were achieved with unhindered alkylamines (Table 2, compounds **5a**–**e**, **6a**, **6b**) and anilines (**5i**, **5j**, **5m**, **5n**, **5o**, **6c**). Several different substituents tolerated the reaction conditions. It is noteworthy that bromo-substituted substrates afforded in good yields the corresponding compounds **5m** and **5n**, which could be used for further cross-coupling transformations. The reaction, however, turned out to be sensitive to steric hindrance. α-Branched product **7** (46% isolated, *conditions A*) rather than the corresponding 1,4-benzoxazine **5h**.[23] When Cs_2CO_3 was used instead of K_3PO_4 (*conditions B*), a higher yield of **7** (52%) was obtained and no cyclization product was detected, either. We attempted to improve this situation by varying of the reaction temperature and by employing different supporting ligands, such as L-proline, ethylene glycol, and 1,10-phenanthroline. In all cases tested the reaction did not proceed at the temperature below 85 °C, while only the side-reaction took place at the elevated temperatures. The structures of representative compounds **5o** and **6c** were confirmed by X-ray single crystal diffraction (Fig. 2).[24]

3. Conclusion

In summary, we have developed a new general approach for the library synthesis of *N*-substituted 4*H*-1,4-benzoxazine-2-carboxylates and 4*H*-1,4-benzothiazine-2-carboxylates from readily available *o*-bromo(thio)phenoxyacetates and primary amines. A number of groups including alkoxy, fluoro, bromo, cyclopropyl, alkoxycarbonyl are well-tolerated in the reaction conditions. This

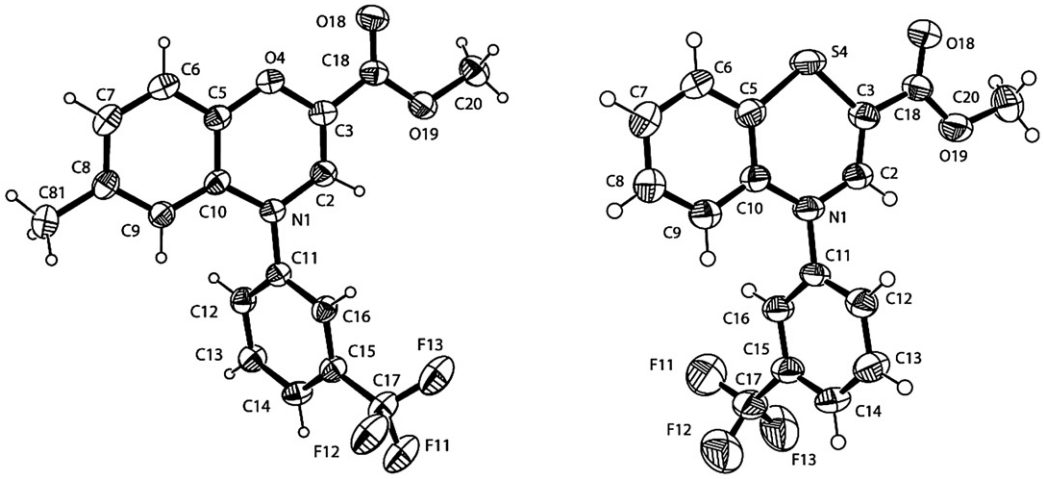


Fig. 2. ORTEP diagrams of **5o** (right) and **6c** (left).

method uses inexpensive CuI as the catalyst without any need for a ligand. This protocol offers significant advantages compared to former methods and opens opportunities for exploration of the practical applications of unsaturated 1,4-benzoxazines and 1,4-benzothiazines in medicinal chemistry.

4. Experimental

4.1. General information

All commercial chemicals were used without further purification. Solvents were distilled prior to use. Column chromatography was carried out on silica gel (40–60 μm). Analytical TLC was performed on pre-coated plates of silica gel 60; visualization was accomplished by UV light (254 nm). Yields refer to chromatographically and spectroscopically pure compounds. Melting points were determined in open-ended capillaries and are uncorrected. IR spectra were obtained with KBr pellets (for solids) or neat liquids; only significant absorptions are listed in cm^{-1}. ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded for $CDCl_3$ or DMSO-d_6 solutions; NMR chemical shifts (δ) are reported in parts per million (ppm) relative to residual peaks of the solvent. The *J* values are given in hertz. Mass-spectra were recorded by EI mode with 70 eV. All reactions were carried out under an air atmosphere. Methyl esters of 2-bromophenoxyacetic,[25] 2-bromo-4-methylphenoxyacetic,[26] 2-bromo-5-fluorophenoxyacetic,[27] and 2-bromophenylthioacetic[25] acids were prepared starting from the corresponding sodium phenoxides or thiophenoxide and methyl 2-bromoacetate.

4.2. Methyl 3-bromo-4-(2-methoxy-2-oxoethoxy)benzoate

A solution of methyl 3-bromo-4-hydroxybenzoate (10.4 g, 45 mmol) in 30 mL of DMF was added dropwise to a pre-cooled (0–5 °C) suspension of NaH (1.9 g, 48 mmol, 60% oil dispersion) in 40 mL of DMF with vigorous stirring. The reaction mixture was stirred at 0 °C for 15 min. A solution of methyl 2-bromoacetate (7.5 g, 4.65 mL, 50 mmol) in 8 mL of DMF was slowly added with continuous stirring. The reaction mixture was warmed to room temperature and was stirred until the starting phenol was consumed as indicated by TLC. A small amount of AcOH (~1 mL) was added and the solvent was evaporated under reduced pressure and the residue was portioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with 50 mL of CH_2Cl_2. The organic extracts were combined and washed with a solution of K_2CO_3 (10%, 100 mL) and with brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated to give a crude product, which recrystallized from MeOH to give 12.00 g (88%) as a white solid, mp 121–123 °C (MeOH). ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 3.88 (s, 3H), 4.77 (s, 2H), 6.77 (d, *J*=8.5 Hz, 1H), 7.94 (dd, *J*=2.1, 8.5 Hz, 1H), 8.25 (d, *J*=2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 51.8, 52.1, 65.5, 111.6, 111.7, 124.5, 129.9, 134.8, 157.4, 165.3, 167.7; MS (*m*/*z*) 304, 302 (M^+ 13, 13), 273, 271 (12, 12), 223 (100), 75 (29). Anal. Calcd for $C_{11}H_{11}BrO_5$: C, 43.59; H, 3.66. Found: C, 43.51; H, 3.72.

4.3. General procedure for the synthesis of methyl 2-(2-Bromophenoxy)-3-oxopropanoates 1 and methyl 2-(2-bromothiophenoxy)-3-oxopropanoate (2)

To a stirred solution of the corresponding (thio)phenoxyacetate (50 mmol) in methyl formate (75 mL) a suspension of sodium hydride (8.0 g 200 mmol, 60% oil dispersion) was slowly added over 1 h at 10–15 °C. After the mixture was stirred for an additional hour it was treated with iced water (300 mL) and two layers were separated. The aqueous layer was acidified with 10% solution of HCl and then extracted with ethyl acetate (3×150 mL). The organic layers were combined, washed successively with water (2×100 mL), saturated solution of $NaHCO_3$ (2×200 mL), and finally with brine (100 mL). The ethyl acetate solution was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure and the residue was dried under vacuum at 0.5 Torr for 3 h. The crude product was obtained as a mixture of isomers with sufficient purity (≥95% by GC/MS) for use in the next reactions without additional purification.

*4.3.1. Methyl 2-(2-bromophenoxy)-3-oxopropanoate (**1a**).* A light yellow viscous liquid, 10.2 g (74%), 60% of major isomer; ^1H NMR ($CDCl_3$, for the major isomer) δ 3.79 (s, 3H), 6.79–7.04 (m, 3H), 7.20–7.24 (m, 1H), 7.54–7.60 (m, 1H), 10.4 (d, *J*=13.1 Hz, 1H); MS (*m*/*z*) 274, 272 (M^+; 30, 30), 246, 244 (10, 10), 193 (99), 199 (60), 161 (40). Anal. Calcd for $C_{10}H_9BrO_4$: C, 43.98; H, 3.32. Found: C, 43.95; H, 3.34.

*4.3.2. Methyl (2-bromo-4-methylphenoxy)-3-oxopropanoate (**1b**).* A light yellow viscous liquid, 10.6 g (74%), 60% of major isomer; ^1H NMR ($CDCl_3$, for the major isomer) δ 2.30 (s, 3H), 3.78 (s, 3H), 6.72 (d, *J*=8.6 Hz, 1H), 7.39–7.44 (m, 2H), 7.36 (d, *J*=13.1 Hz, 1H), 10.29 (d, *J*=13.1 Hz, 1H); MS (*m*/*z*) 288, 286 (M^+; 34, 34), 260, 258 (12, 12), 207 (100), 199 (60). Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.02; H, 3.86. Found: C, 46.05; H, 3.84.

*4.3.3. Methyl 3-bromo-4-(1-formyl-2-methoxy-2-oxoethoxy)benzoate (**1c**).* A light yellow viscous liquid, 11.6 g (70%), 62% of major isomer; ^1H NMR (DMSO-d_6, for the major isomer) δ 3.64 (s, 3H),

3.83 (s, 3H), 6.96 (d, J=8.6 Hz, 1H), 7.72 (s, 1H), 7.88 (dd, J=8.7, 1.8 Hz, 1H), 8.12 (d, J=1.8 Hz, 1H); MS (m/z) 334, 332 (M^+ 13, 13), 251 (52), 219 (27), 75 (78), 59 (100). Anal. Calcd for $C_{12}H_{11}BrO_6$: C, 43.53; H, 3.35. Found: C, 43.55; H, 3.34.

*4.3.4. Methyl 2-(2-bromo-5-fluorophenoxy)-3-oxopropanoate (**1d**).* A light yellow viscous liquid, 11.3 g (78%), 65% of major isomer; ^{1}H NMR ($CDCl_3$, for the major isomer) δ 3.79 (s, 3H), 6.57–6.72 (m, 3H), 7.49–7.55 (m, 1H), 10.9 (d, J=12.4 Hz, 1H); MS (m/z) 292, 290 (M^+; 27, 27), 264, 262 (14, 14), 211 (98), 203 (60). Anal. Calcd for $C_{10}H_8BrFO_4$: C, 41.26; H, 2.77. Found: C, 41.25; H, 2.74.

*4.3.5. Methyl 2-[(2-bromophenyl)thio]-3-oxopropanoate (**2**).* A light yellow viscous liquid, 12.7 g (88%), 95% of major isomer; NMR ^{1}H ($CDCl_3$, for the major isomer): δ 3.81 (s, 3H), 6.96 (dd, J=7.8, 1.27 Hz, 1H), 7.03 (td, J=7.6, 1.52 Hz, 1H), 7.25 (td, J=6.6, 1.26 Hz, 1H), 7.52 (dd, J=7.8, 1.1 Hz, 1H), 7.75 (d, J=13.1 Hz, 1H), 12.5 (d, J=13.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 52.3, 95.0, 119.9, 125.4, 126.0, 127.3, 132.5, 138.6, 171.5, 172.3. MS (m/z): 290, 288 (M^+; 40, 40), 262, 260 (M^+, 12, 12), 209 (M^+, 100), 201 (60), 177 (40), 149 (90), 108 (25), 91 (95). Anal. Calcd for $C_{10}H_9BrO_3S$: C, 41.54; H, 3.14. Found: C, 41.55; H, 3.12.

4.4. General one-pot procedure for the synthesis of *N*-substituted methyl 1,4-benzoxazine-2-carboxylates 5 and 1,4-benzothiazine-2-carboxylates 6

A reaction tube with a stir bar was charged with the corresponding formyl ester **1** or **2** (3 mmol) and MeOH (5 mL). An appropriate amine (3 mmol) was added to the resulted solution and the whole mixture was stirred for 10 h at ambient temperature (for alkylamines) or for 3 h at reflux (for anilines). A crystalline precipitate was formed in some cases. The tube was attached to a vacuum line and the solvent was evaporated to dryness. The residue was redissolved in DMF (3 mL) and to the solution CuI (57 mg, 0.3 mmol, 10 mol %) and K_3PO_4 (1.27 g, 6 mmol) or Cs_2CO_3 (1.95 g, 6 mmol) were added. The tube was sealed and the mixture was allowed to stir vigorously at 110 °C for 16 h (K_3PO_4, *conditions A*) or at 85 °C for 8 h (Cs_2CO_3, *conditions B*). After completion of the reaction, the mixture was cooled to room temperature and the solvent was evaporated to dryness under reduced pressure. Water (15 mL) was added to the residue and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with 10% solution of HCl (15 mL), and with brine (15 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography (hexane/ethyl acetate, 20/1) provided the corresponding product **5**or **6**.

*4.4.1. Methyl 4-benzyl-6-methyl-4H-1,4-benzoxazine-2-carboxylate (**5a**).* Reaction of benzylamine (321 mg, 3 mmol) and **1b** (861 mg, 3 mmol) according to the general procedure afforded 770 mg (87%, *conditions A*) or 750 mg (85%, *conditions B*) of **5a**, isolated as a yellow crystalline solid: mp 123–125 °C. IR (KBr) ν_{max} 1654, 1697. ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 3.75 (s, 3H), 4.42 (s, 2H), 6.06 (s, 1H), 6.45–6.53 (m, 2H), 6.57 (s, 1H), 7.27–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.8, 51.6, 53.3, 113.6, 115.7, 124.1, 125.4, 126.6 (2C), 127.8, 129.0 (2C), 129.1, 131.1, 133.7, 135.8, 144.0, 162.3; MS m/z (%) 295 (M^+, 10), 205 (55), 91 (100), 65 (45). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.21; H, 5.72; N, 4.68.

*4.4.2. Methyl 4-benzyl-7-fluoro-4H-1,4-benzoxazine-2-carboxylate (**5b**).* Reaction of benzylamine (321 mg, 3 mmol) and **1d** (873 mg, 3 mmol) according to the general procedure afforded 736 mg (82%, *conditions A*) of **5b**, isolated as a brown crystalline solid: mp 138–141 °C. IR (KBr) ν_{max} 1087–1455, 1656, 1702. ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 4.41 (s, 2H), 6.10–6.12 (m, 1H), 6.26–6.33 (m, 1H), 6.38–6.42 (m, 1H), 6.62 (s, 1H), 7.30–7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 51.1, 53.4, 104.3 (d, J_{C-F}=27.6 Hz), 108.5 (d, J_{C-F}=22.4 Hz), 112.5 (d, J_{C-F}=9.2 Hz), 124.0, 126.1 (2C), 127.2, 127.6, 128.7 (2C), 129.1, 134.9, 146.9 (d, J_{C-F}=11.9 Hz), 158.8 (d, J_{C-F}=243 Hz), 161.5; MS m/z (%) 293 (M+, 30), 208 (95), 137 (15), 121 (15), 91 (100). Anal. Calcd for $C_{17}H_{14}FNO_3$: C, 68.22; H, 4.71; N, 4.68. Found: C, 68.21; H, 4.72; N, 4.60.

*4.4.3. Dimethyl 4-benzyl-4H-1,4-benzoxazine-2,6-dicarboxylate (**5c**).* Reaction of benzylamine (321 mg, 3 mmol) and **1c** (993 mg, 3 mmol) according to the general procedure afforded 732 mg (76%, *conditions A*) of **5c**, isolated as a yellow crystalline solid: mp 154–157 °C. IR (KBr) ν_{max} 1655, 1708. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 3H), 3.82 (s, 3H), 4.44 (s, 2H), 6.22 (d, J=8.4 Hz, 1H), 6.54 (s, 1H), 7.22 (d, J=1.8 Hz, 1H), 7.31–7.42 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 29.7, 52.0, 53.5, 112.0, 113.4, 115.6, 116.5, 126.5 (2C), 126.7, 128.1, 128.2, 129.0, 129.2 (2C), 136.3, 146.0, 161.8, 165.8; MS m/z (%) 339 (M^+, 13), 248 (47), 91 (100). Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.21; H, 5.07; N, 4.14.

*4.4.4. Methyl 6-methyl-4-(2-phenylethyl)-4H-1,4-benzoxazine-2-carboxylate (**5d**).* Reaction of (2-phenylethyl)amine (363 mg, 3 mmol) and **1b** (861 mg, 3 mmol) according to the general procedure afforded 798 mg (86%, *conditions A*) of **5d**, isolated as a yellow crystalline solid: mp 92–95 °C. IR (KBr) ν_{max} 1670, 1712. ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.93 (d, J=7.3 Hz, 2H), 3.42 (d, J=7.3 Hz, 2H), 3.72 (s, 3H), 6.19 (s, 1H), 6.31 (s, 1H), 6.47–6.54 (m, 2H), 7.20–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 20.9, 33.5, 51.2, 51.4, 112.9, 115.8, 124.0, 125.0, 126.8, 128.7, 128.8 (4C), 128.9, 130.5, 133.3, 137.9, 144.0, 162.2. MS m/z (%) 309 (M^+, 16), 218 (100), 130 (20), 91 (53). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.71; H, 6.12; N, 4.58.

*4.4.5. Methyl 4-(tetrahydrofuran-2-ylmethyl)-4H-1,4-benzoxazine-2-carboxylate (**5e**).* Reaction of (tetrahydrofuran-2-ylmethyl)amine (304 mg, 3 mmol) and **1a** (862 mg, 3 mmol) according to the general procedure afforded 594 mg (72%, *conditions A*) of **5e**, isolated as a yellow oil. IR (neat) ν_{max} 1662, 1711. ^{1}H NMR ($CDCl_3$) δ 1.56–1.65 (m, 1H), 1.89–2.11 (m, 3H), 3.20–3.35 (m, 2H), 3.75 (s, 3H), 3.77–3.83 (m, 1H), 3.89–3.95 (m, 1H), 4.09–4.17 (m, 1H), 6.35–6.41 (m, 1H), 6.55–6.61 (m, 2H), 6.65–6.73 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 25.7, 29.2, 51.5, 53.3, 68.3, 76.1, 111.9, 114.6, 116.3, 116.0, 123.7, 124.1, 125.0, 129.5, 146.3, 162.3. MS m/z (%): 275 (M^+, 39), 204 (100), 71 (59), 43 (87). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: 65.46; H, 6.21; N, 5.08.

*4.4.6. Methyl 4-(1-phenylethyl)-4H-1,4-benzoxazine-2-carboxylate (**5f**).* Reaction of (*R*)-(+)-1-phenylethylamine ($[\alpha]_D^{20}$ +40.0 (neat)) (363 mg, 3 mmol) and **1b** (861 mg, 3 mmol) according to the general procedure afforded 398 mg (45%, *conditions A*) or 486 mg (55%, *conditions B*) of **5f**, isolated as a yellow oil. $[\alpha]_D^{23}$ +18.5 (*c* 1, CH_2Cl_2). IR (neat) ν_{max} 1659, 1719. ^{1}H NMR ($CDCl_3$) 1.66 (d, J=6.8 Hz, 3H), 3.77 (s, 3H), 4.81 (q, J=6.9 Hz, 1H), 6.32–6.39 (m, 1H), 6.61–6.72 (m, 3H), 6.75 (s, 1H), 7.29–7.47 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.4, 50.4, 54.1, 111.7, 114.9, 122.6, 122.8, 123.7, 124.8, 125.0 (2C), 126.6, 127.7, 127.9 (2C), 139.5, 161.1; MS m/z (%) 295 (M^+, 5), 105 (100), 77 (23), 51 (16). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.21; H, 7.72; N, 4.68.

*4.4.7. Methyl 4-cyclohexyl-4H-1,4-benzoxazine-2-carboxylate (**5g**).* Reaction of cyclohexylamine (297 mg, 3 mmol) and **1b** (861 mg, 3 mmol) according to the general procedure afforded 319 mg (39%, *conditions A*) or 434 mg (53%, *conditions B*) of **5g**, isolated as a yellow oil. IR (neat) ν_{max} 1654, 1723. ^{1}H NMR ($CDCl_3$) δ 1.31–1.46 (m, 4H), 1.69–1.82 (m, 2H), 1.86–1.99 (m, 4H), 3.30–3.40 (m, 1H), 3.77 (s, 3H), 6.41 (d, J=7.6 Hz, 1H), 6.59–6.65 (m, 1H), 6.72–6.77 (m, 1H), 6.86–6.91 (m, 1H), 6.98–7.03 (m, 1H). ^{13}C

NMR ($CDCl_3$) δ 25.5, 25.7 (2C), 30.8 (2C), 51.5, 55.2, 111.7, 113.6, 116.3, 123.7, 123.8, 124.7, 129.5, 146.9, 162.3; MS *m*/*z* (%) 273 (M^+, 26), 191 (79), 176 (22), 132 (48), 103 (18), 83 (26), 55 (100). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.25; H, 7.02; N, 5.18.

*4.4.8. Methyl 4-(4-methoxyphenyl)-6-methyl-4H-1,4-benzoxazine-2-carboxylate (**5i**).* Reaction of 4-methoxyaniline (369 mg, 3 mmol) and **1b** (861 mg, 3 mmol) according to the general procedure afforded 765 mg (82%, *conditions A*) of **5i**, isolated as a light brown crystalline solid: mp 98–100 °C. IR (KBr) ν_{max} 1662, 1710. ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 3.77 (s, 3H), 3.87 (s, 3H), 5.93 (s, 1H), 6.49–6.54 (m, 1H), 6.56–6.60 (m, 1H), 6.65 (s, 1H), 7.00 (d, *J*=9.1 Hz, 2H), 7.24 (d, *J*=9.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 20.7, 51.6, 55.6, 114.6, 115.4 (2C), 116.0, 124.5, 125.7, 128.3 (2C), 128.5, 132.3, 133.2, 133.8, 143.3, 158.9, 162.4. MS *m*/*z* (%) 311 (M^+, 78), 252 (100), 180 (35), 91 (45). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.40; H, 5.56; N, 4.58.

*4.4.9. Dimethyl 4-(4-methoxyphenyl)-4H-1,4-benzoxazine-2,6-dicarboxylate (**5j**).* Reaction of 4-methoxyaniline (369 mg, 3 mmol) and **1c** (993 mg, 3 mmol) according to the general procedure afforded 948 mg (89%, *conditions A*) of **5j**, isolated as a yellow crystalline solid: mp 105–107 °C. IR (KBr) ν_{max} 1674, 1709. ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.09 (d, *J*=8.11 Hz, 1H), 6.59 (s, 1H), 7.00 (d, *J*=8.99 Hz, 2H), 7.24 (d, *J*=8.99 Hz, 2H), 7.27–7.32 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 51.8, 52.0, 55.6, 113.0, 115.6 (2C), 117.0, 126.0, 126.4, 126.6, 127.7, 128.1 (2C), 133.1, 137.4, 145.4, 159.3, 161.2, 165.9. MS *m*/*z* (%) 355 (M^+, 56), 296 (60), 188 (47), 59 (100). Anal. Calcd for $C_{19}H_{16}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.30; H, 4.86; N, 3.98.

*4.4.10. Methyl 4-mesityl-4H-1,4-benzoxazine-2-carboxylate (**5k**).* Reaction of mesitylamine (405 mg, 3 mmol) and **1a** (819 mg, 3 mmol) according to the general procedure afforded 537 mg (58%, *conditions A*) or 584 mg (63%, *conditions B*) of **5 k**, isolated as a tan crystalline solid: mp 158–160 °C. IR (KBr) ν_{max} 1660, 1716. ^1H NMR ($CDCl_3$) δ 2.30–2.36 (m, 9H), 3.76 (s, 3H), 5.70 (dd, *J*=8.1, 1.5 Hz, 1H), 6.42 (s, 1H), 6.51–6.57 (m, 1H), 6.63–6.71 (m, 2H), 6.98 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 17.3 (2C), 20.6, 51.1, 112.4, 115.7, 123.5, 123.8, 125.0, 127.9, 129.4 (2C), 131.0, 134.3, 136.8 (2C), 138.2, 145.3, 161.9. MS *m*/*z* (%) 309 (M^+, 85), 250 (14), 222 (49), 190 (36). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.71; H, 6.17; N, 4.58.

*4.4.11. Methyl 4-(1-naphthyl)-4H-1,4-benzoxazine-2-carboxylate (**5l**).* Reaction of 1-naphtylamine (423 mg, 3 mmol) and **1a** (819 mg, 3 mmol) according to the general procedure afforded 447 mg (47%, *conditions A*) or 600 mg (63%, *conditions B*) of **5l**, isolated as a brown crystalline solid: mp 150–154 °C. IR (KBr) ν_{max} 1663, 1716. ^1H NMR ($CDCl_3$) δ 3.77 (s, 3H), 5.76 (dd, *J*=7.8, 1.1 Hz, 1H), 6.50 (td, *J*=7.9, 2.0 Hz, 1H), 6.68–6.78 (m, 3H), 7.52–7.62 (m, 4H), 7.78–7.88 (m, 1H), 7.91–8.00 (m, 2H), 8.15–8.22 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 51.2, 113.9, 115.9, 122.6, 123.4, 124.1, 125.4, 125.5, 125.8, 126.5, 127.0, 128.3, 128.5, 128.7, 130.1, 132.6, 134.6, 136.9, 145.0, 161.9; MS *m*/*z* (%) 317 (M^+, 93), 258 (50), 228 (29), 202 (26), 180 (31), 152 (29), 127 (100). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.7; H, 4.76; N, 4.41. Found: C, 75.71; H, 4.72; N, 4.48.

*4.4.12. Methyl 4-(3-bromophenyl)-4H-1,4-benzoxazine-2-carboxylate (**5m**).* Reaction of 3-bromoaniline (516 mg, 3 mmol) and **1a** (819 mg, 3 mmol) according to the general procedure afforded 747 mg (72%, *conditions A*) of **5m**, isolated as a light brown crystalline solid: mp 142–145 °C. IR (KBr) ν_{max} 1670, 1712. ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 6.30 (dd, *J*=7.84, 1.27 Hz, 1H), 6.67 (td, *J*=7.33 Hz, 1.52, 1H), 6.71–6.82 (m, 3H), 7.27–7.31 (m, 1H), 7.85 (t, *J*=7.83 Hz, 1H), 7.46–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 51.3, 113.4, 116.4, 116.8, 118.6, 123.4, 123.4, 124.7, 126.1, 126.6, 128.7, 130.1, 130.2, 131.0, 145.3, 161.7; MS (I, %): 347, 345 (M^+, 28, 28), 288, 286 (24, 24), 207 (12), 179 (30), 152 (31), 119 (18), 76 (100). Anal. Calcd for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05. Found: C, 55.61; H, 3.42; N, 4.08.

*4.4.13. Dimethyl 4-(3-bromophenyl)-4H-1,4-benzoxazine-2,6-dicarboxylate (**5n**).* Reaction of 3-bromoaniline (321 mg, 3 mmol) and **1c** (993 mg, 3 mmol) according to the general procedure afforded 884 mg (73%, *conditions A*) of **5n**, isolated as a yellow crystalline solid: mp 158–160 °C. IR (KBr) ν_{max} 1674, 1718. ^1H NMR ($CDCl_3$) δ 3.79 (s, 3H), 3.85 (s, 3H), 6.25 (d, *J*=8.24 Hz, 1H), 6.65 (s, 1H), 7.26–7.30 (m, 1H), 7.32–7.41 (m, 3H), 7.49–7.54 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 51.9, 52.1, 113.1, 117.5, 123.7, 124.9, 126.2, 126.4, 126.7, 127.5, 129.4, 131.2, 131.6, 136.1, 141.6, 145.4, 161.7, 165.7; MS *m*/*z* (%) 403, 405 (M^+, 43), 346, 344 (42, 42), 265 (17), 151 (36), 75 (100). Anal. Calcd for $C_{18}H_{14}BrNO_5$: C, 53.49; H, 3.49; N, 3.47. Found: C, 53.51; H, 3.42; N, 3.48.

*4.4.14. Methyl 6-methyl-4-[3-(trifluoromethyl)phenyl]-4H-1,4-benzoxazine-2-carboxylate (**5o**).* Reaction of 3-trifluoromethylaniline (483 mg, 3 mmol) and **1b** (861 mg, 3 mmol) according to the general procedure afforded 753 mg (72%, *conditions A*) of **5o**, isolated as a light brown crystalline solid: mp 130–132 °C. IR (KBr) ν_{max} 1097–1454, 1671, 1702. ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H), 3.76 (s, 3H), 6.05 (s, 1H), 6.53–6.64 (m, 2H), 6.73 (s, 1H), 7.49–7.67 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 20.7, 51.7, 114.4, 116.6, 122.9, 123.4 (J_{C-F}=271 Hz) 123.9, 125.3, 126.6, 127.1, 129.4, 130.8, 130.9, 132.7 (J_{C-F}=34 Hz), 133.6, 141.6, 143.4, 162.1; MS *m*/*z* (%) 349 (M^+, 100), 290 (90), 145 (40). Anal. Calcd for $C_{18}H_{14}F_3NO_3$: C, 61.89; H, 4.04; N, 4.01. Found: C, 61.85; H, 4.07; N, 4.08.

*4.4.15. Methyl 4-benzyl-4H-1,4-benzothiazine-2-carboxylate (**6a**).* Reaction of benzylamine (321 mg, 3 mmol) and **2** (867 mg, 3 mmol) according to the general procedure afforded 641 mg (72%, *conditions A*) of **6a**, isolated as an orange crystalline solid: mp 98–100 °C. IR (KBr) ν_{max} 1631, 1683. ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H), 4.63 (s, 2H), 6.34–6.43 (m, 1H), 6.72–6.85 (m, 3H), 7.18 (s, 1H), 7.24–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 52.0, 55.3, 114.0, 121.5, 125.0, 126.4 (2C), 127.4, 127.5, 127.9, 129.1 (2C), 135.6, 139.9, 144.2, 164.1; MS *m*/*z* (%) 297 (M^+, 10), 207 (95), 147 (15), 91 (100). Anal. Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.60; H, 5.07; N, 4.68.

*4.4.16. Methyl 4-cyclopropyl-4H-1,4-benzothiazine-2-carboxylate (**6b**).* Reaction of cyclopropylamine (171 mg, 3 mmol) and **2** (867 mg, 3 mmol) according to the general procedure afforded 570 mg (77%, *conditions A*) or 578 mg (78%, *conditions B*) of **6b**, isolated as a light brown solid: mp 102–105 °C. IR (KBr) ν_{max} 1683. ^1H NMR ($CDCl_3$) δ 0.8–0.85 (m, 2H), 0.97–1.03 (m, 2H), 2.66–2.72 (m, 1H), 3.77(s, 3H), 6.85–6.91 (m, 2H), 6.97–7.05 (m, 2H), 7.38 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 7.8 (2C), 32.0, 51.1, 95.2, 113.8, 120.6, 124.4, 126.8, 126.9, 141.1, 144.3, 163.5; MS *m*/*z* (%) 247 (M^+, 65), 216 (10), 206 (15), 188 (80), 154(100). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.21; H, 5.32; N, 5.68.

*4.4.17. Methyl 4-[3-(trifluoromethyl)phenyl]-4H-1,4-benzothiazine-2-carboxylate (**6c**).* Reaction of 3-trifluoromethylaniline (483 mg, 3 mmol) and **2** (867 mg, 3 mmol) according to the general procedure afforded 768 mg (73%, *conditions A*) or 768 mg (73%, *conditions B*) of **6c**, isolated as an orange crystalline solid: mp 127–129 °C. IR (KBr) ν_{max} 1076–1477, 1677. ^1H NMR ($CDCl_3$) δ 3.78(s, 3H), 6.05 (d, *J*=7.0 Hz, 2H), 6.77–6.93 (m, 3H), 7.33 (s, 1H), 7.53–7.73 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 52.2, 97.4, 115.4, 121.0, 123.1 (J_{C-F}=275 Hz), 124.4 (J_{C-F}=3.7 Hz), 124.9 (J_{C-F}=3.7 Hz), 125.6, 127.4, 127.8, 130.9, 131.3,

133.1 (J_{C-F}=33 Hz), 141.0, 142.1, 143.2, 164.0; MS *m*/*z* (%) 351 (M^+, 80), 292 (100), 223 (40), 121 (90). Anal. Calcd for $C_{17}H_{12}F_3NO_2S$: C, 58.11; H, 3.44; N, 3.99. Found: C, 58.09; H, 3.42; N, 3.98.

*4.4.18. Methyl 3-(tert-butylamino)-2-(4-methylphenoxy)acrylate (**7**).* Reaction of *tert*-butylamine (219 mg, 3 mmol) and **1b** (861 mg, 3 mmol) according to the general procedure afforded 362 mg (46%, *conditions A*) or 410 mg (52%, *conditions B*) of **7**, isolated as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9H), 2.31 (s, 3H), 3.68 (s, 3H), 4.62 (d, *J*=13.8 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 2H), 7.09 (d, *J*=8.4 Hz, 2H), 7.46 (d, *J*=13.8, 1H). ^{13}C NMR ($CDCl_3$) δ 20.6, 29.0, 50.0, 51.8, 114.7 (2C), 121.0, 128.5 (2C), 129.3, 130.0, 149.8, 161.1; MS *m*/*z* (%) 263 (M^+, 41), 205 (35), 148 (100), 119 (67). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.35; H, 8.12; N, 5.38.

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