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A general and efficient PIFA mediated synthesis of heterocycle-fused quinolinone derivatives

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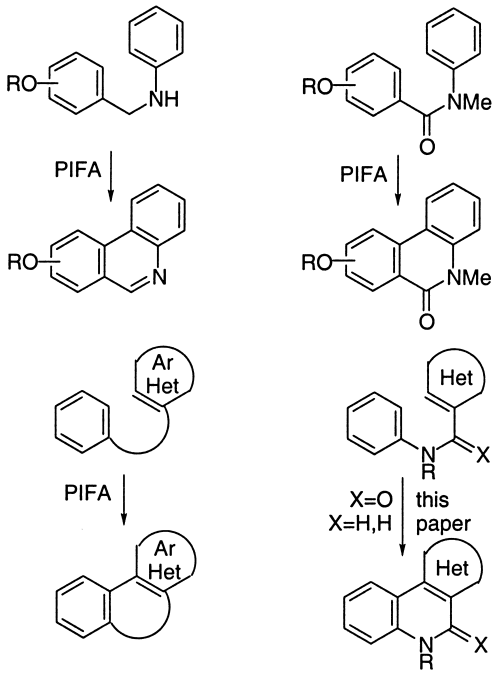
Abstract—A new application of the hypervalent iodine reagent phenyliodine(III)bis(trifluoroacetate) (PIFA) has been developed for the construction of a series of *N*, *O*, *S*-containing heterocycle-fused quinolinone derivatives in a general and efficient way. An alternative approach to the formation of these novel tricyclic heterocycles by a PIFA mediated aryl–heteroaryl coupling reaction is also presented.

1. Introduction

In the last decades the chemistry of hypervalent iodine reagents has witnessed a profound progress in the field of synthetic organic chemistry. Their low toxicity, ready availability and easy handling have allowed their application to a number of important transformations[1] and, besides, their environmentally friendly nature also suggests future applications in 'green chemistry'. Particularly, phenyliodine(III)*bis*(trifluoroacetate) (PIFA), phenyliodine(III)diacetate) (PIDA) and hydroxy(tosyloxy)iodobenzene, Koser's reagent (HITB) have found a wide application in the synthesis of heterocyclic compounds.[2] Among them, the known PIFA-mediated biaryl coupling reaction has been employed by us[3] and by others[4] for the preparation of different synthetic and naturally occurring products containing the biaryl moiety. By contrast, apart from the initial results of our group,[5] and despite of its enormous potential in the area of heterocyclic chemistry, the I(III) promoted aryl–heteroaryl coupling reaction has not been studied. Thus, according to this strategy, we have employed PIFA to generate aryl radical-cations, via a SET mechanism,[6] to be intramolecularly trapped by aromatic and heteroaromatic rings giving rise to a series of phenanthridines, phenanthridinones[3a] and phenanthrenoids[5a] starting from *N*-arylbenzylamines, *N*-arylbenzamides and stilbenoids, respectively (see Scheme 1).

The quinoline system is a prevalent topic of research. Its presence in a variety of biologically active compounds[7] has led to the design of numerous approaches towards the construction of this skeleton.[8] In particular, some naturally occurring and synthetically produced heterocycle-fused quinolines and quinolinones of type **1** have attracted the interest of the research community on account of their important activity.[9] However, there is a lack of effective and general routes for the synthesis of this kind of derivatives.



Scheme 1.

Keywords: hypervalent iodine; heterocycles; cyclizations; biaryl coupling; quinolinones.

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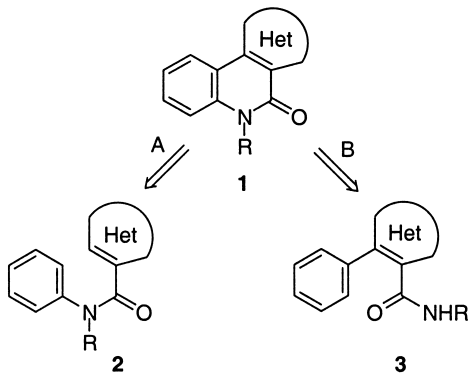


Scheme 2.

Therefore, and according to the success reached in our previous experience, we decided to expand that methodology to the preparation of heterocycle-fused quinoline and quinolinone derivatives from precursors of type **2** (see approach A in Scheme 2).

On the other hand, during the course of our investigations several problems arisen (vide infra) and, therefore, an alternative synthetic approach had to be evaluated (see approach B in Scheme 2). Encouraged by the enormous synthetic potential of hypervalent iodine reagents, conveniently functionalized synthons **3** containing a preformed biaryl bond were prepared. On the residual carboxamide group, a PIFA mediated oxidation reaction was envisaged to perform the key cyclization step. Therefore, in this paper, a study of the I(III) mediated synthesis of a series of heterocycle-fused quinolinones **1** will be disclosed through the already mentioned routes.

2. Results and discussion

2.1. The biaryl coupling approach

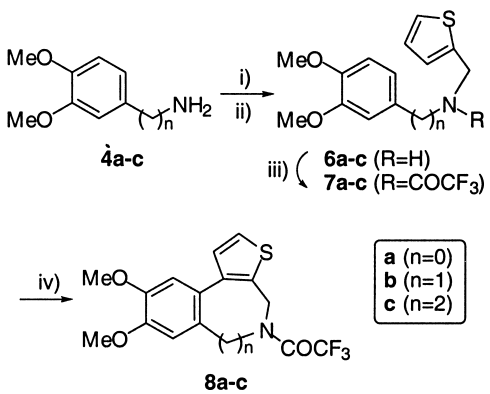
In order to optimize the projected approach (A in Scheme 2), the thiophene ring was selected as the heterocyclic partner on the basis of its demonstrated stability under oxidative coupling conditions.[5] Thus, substrates **7a–c** (n=0,1,2) were prepared as follows (see Scheme 3). The reaction between commercially available amines **4a–c** and 2-thiophene-carboxaldehyde (**5**) gave rise to the corresponding imines which, without isolation (^{1}H NMR=8.2–8.6 ppm), were reduced with $NaBH_4$ to furnish amines **6a–c** which, in turn, were trifluoroacetylated[10] yielding the corresponding amides **7a–c**, in good overall yields (64–72%). Finally, these adequately functionalized precursors were submitted to the cyclization conditions.

The oxidative biaryl-coupling step was accomplished using commercially available PIFA and $BF_3{\cdot}OEt_2$ as the activating agent in CH_2Cl_2 as solvent.[11] Optimization of the experimental conditions (amounts of reagents and reaction temperature) led to the formation of the desired tricyclic compounds, thienobenzoazepine **8b** (n=1) and thienobenzoazocine **8c** (n=2), in moderate yields (47 and 20%, respectively). However, treatment of amide **7a** under a variety of reaction conditions resulted in a complete degradation of the starting material. Consequently, the expected thienoquinolinone **8a** (n=0) was never detected.

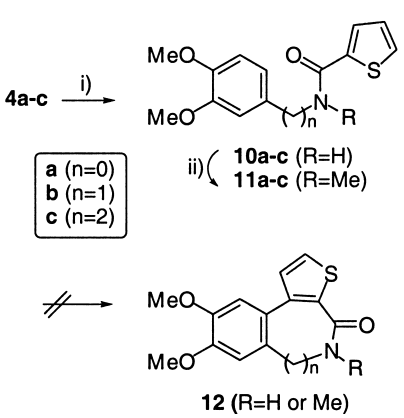
Inspired in our precedents for the PIFA-mediated synthesis of phenanthridinones from *N*-arylbenzamides,[3a] we next checked the behavior of amides of type **10** and **11** under the cyclization conditions. Thus, according to Scheme 4, acylation of amines **4a–c** with 2-thiophenecarbonyl chloride (**9**) yielded amides **10a–c** which were *N*-methylated[12] under standard conditions to afford *N*-methylamides **11a–c**, respectively, in good overall yields (61–90%). Unfortunately, none of the six amides **10** and **11** submitted to the cyclization reaction under a variety of conditions afforded the desired tricyclic derivatives of type **12**. In all cases, degradation of the starting materials to afford complex mixtures of unidentified compounds was observed.

2.2. The aromatic amidation approach

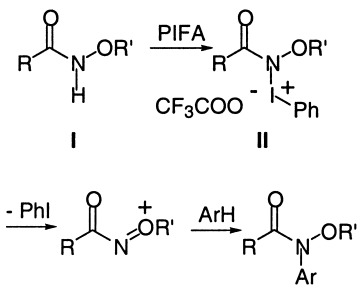
Although, as already mentioned, the synthesis of some of the target molecules **8b**,**c** has been accomplished, we were not satisfied with the obtained results since the employed procedure is far to be considered efficient and general for our synthetic purposes. Therefore, we decided to evaluate the alternative B shown in Scheme 2.[13] In this context, we next focused our attention on the known ability of PIFA to generate *N*-acylnitrenium ions from *N*-alkoxyamides[14]



Scheme 3. (i) 2-Thiophenecarboxaldehyde (**5**), toluene, reflux; (ii) $NaBH_4$, MeOH, 0°Crt (92% for **6a**, 95% for **6b**, 90% for **6c**); (iii) $(CF_3CO)_2O$, pyridine, rt (70% for **7a**, 75% for **7b**, 80% for **7c**); (iv) PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −40−20°C (0% for **8a**, 47% for **8b**, 20% for **8c**).



Scheme 4. (i) 2-Thiophenecarbonyl chloride (**9**), pyridine, CH_2Cl_2, 0°Crt (94% for **10a**, 72% for **10b**, 97% for **10c**); (ii) MeI, NaH, THF, 0°C rt (96% for **11a**, 84% for **11b**, 90% for **11c**).

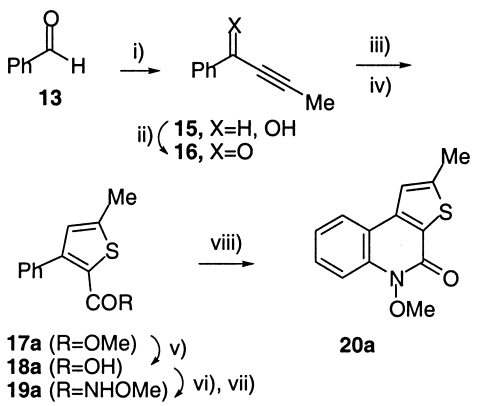


Scheme 5.

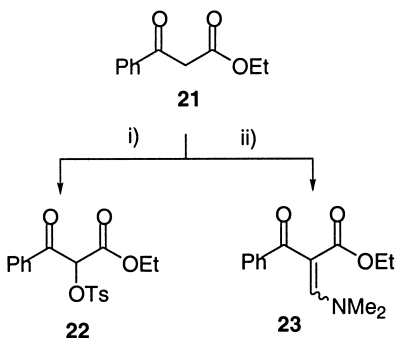
which, eventually, could be trapped intramolecularly by arene rings to afford the target quinoline skeleton in a simple way. Kikugawa had previously employed this approach in an electrophilic aromatic substitution reaction,[15] which involved a *N*-chlorination step with *t*-BuOCl and oxidative cyclization using silver or zinc salts.[16] Similarly, Cherest and Lusinchi employed ferric chloride with the same purpose.[17] Later, it was found[18] that limitations associated with these protocols (i.e. solubility of silver salts or undesired aromatic chlorination) could be overcome by using PIFA as the cyclization reagent in a single step.

It is accepted that *N*-alkoxyamides **I** (see Scheme 5) react with I(III) reagents to give intermediates of type **II**. Subsequently, by release of PhI, the positively charged species generated, which is stabilized by the electron donating alkoxy group, is trapped intra- or intermolecularly by an aromatic group. In our case, we envisaged that starting from a precursor with a preformed biaryl bond and a residual carbamoyl group on the heteroaromatic ring, as in **3**, would facilitate the projected heterocyclization.

Face to comparative purposes, we selected again a thiophene substituted derivative as a model to optimize the cyclization step. The preparation of the required ester **17a** started (see Scheme 6) from benzaldehyde (**13**), which reacted with the commercially available Grignard reagent **14** to afford the propargylic alcohol **15**. Once prepared, it was oxidized with manganese oxide to provide the corresponding ketone **16**[19] which underwent conjugate addition with methyl thioglycolate and subsequent cyclization under basic conditions yielding the methyl ester **17a** in an excellent 87% overall yield (four steps). Next, the ester group was hydrolyzed under basic conditions, and the resulting free carboxylic acid **18a** was transformed into the required amide **19a** by treatment of the corresponding acyl chloride derivative with methoxylamine. When the oxidative cyclization conditions were applied to amide **19a**, the desired quinolinone **20a** was obtained in 37% yield. To our delight, by using TFA instead of $BF_3{\cdot}OEt_2$ as the activating agent,[20] the yield was dramatically increased to 91%.



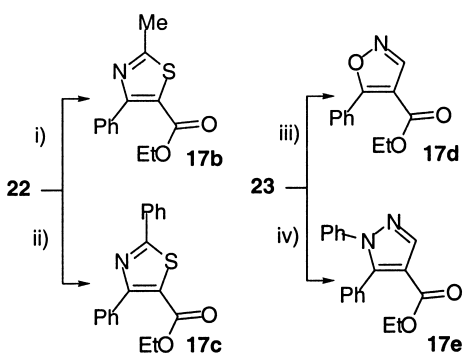
Scheme 6. (i) THF, 1-propynylmagnesium bromide (**14**), 0°C; (ii) MnO_2, CH_2Cl_2, 0°C (92%, two steps); (iii) $HSCH_2CO_2Me$, THF, 0°C; (iv) MeOH, Cs_2CO_3, $MgSO_4$, 0°Crt (97%, two steps); (v) NaOH, MeOH, THF, H_2O, rt (97%); (vi) $SOCl_2$, toluene, reflux; (vii) $NH_2OMe{\cdot}HCl$, pyridine, CH_2Cl_2, 0°Crt; (viii) PIFA, TFA, CH_2Cl_2, 0°Crt (65%, two steps).



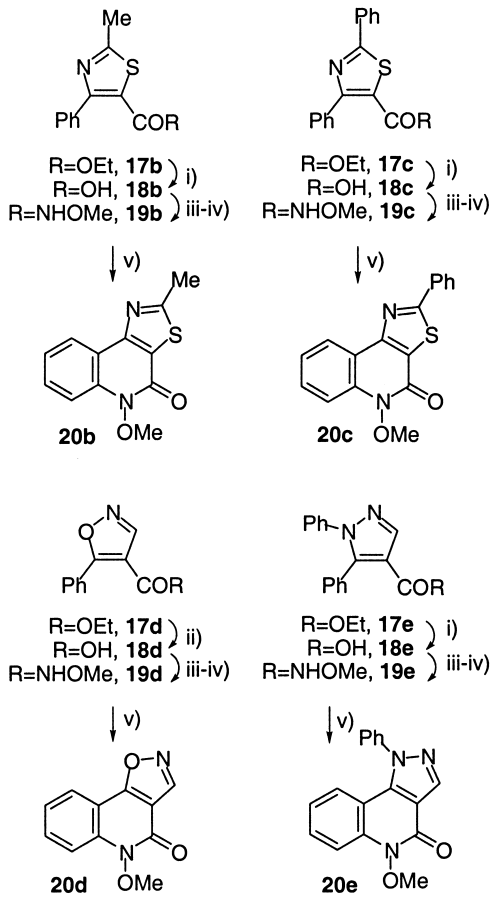
Scheme 7. (i) HITB, MeCN, 75°C (85%); (ii) DMFDMA, toluene, 60°C (92%).

To the light of the so-obtained promising results, and searching for future SAR studies, we decided to expand our synthetic approach to the synthesis of a series of heterocycle-fused quinolinones.[21] With this objective in mind, benzoylacetate **21** was selected as the starting material on the basis of its potentiality for the preparation of a number of different heterocycles (see Scheme 7).[22] Thus, ester **21** was transformed into the synthetically activated tosyloxy derivative **22**[23] by the action of Koser's reagent (HITB)[24] and, separately, into the enaminoester **23** by treatment with dimethylformamide dimethyl acetal (DMFDMA).[25]

Following with our synthetic objectives (see Scheme 8), ketoester **22** was treated independently with thioacetamide and thiobenzamide, under Hantzsch conditions, to afford thiazoles **17b** and **17c**, respectively, in good yields.[26] On the other hand, the action of hydroxylamine[3d] and phenylhydrazine[27] on enaminoester **23** resulted in the formation of the corresponding isoxazole **17d** and phenylpyrazole **17e**, respectively, in good yields.



Scheme 8. (i) $MeCSNH_2$, DMF, 60°C (75%); (ii) $PhCSNH_2$, DMF, 60°C (86%); (iii) $NH_2OH{\cdot}HCl$, pH=4−5, MeOH, 115°C, sealed tube (80%); (iv) $PhNHNH_2$, pH=5–6, MeOH, reflux (91%).



Scheme 9. (i) NaOH, H_2O, MeOH, rt (87% for **18b**, 93% for **18c**, 85% for **18e**); (ii) HCl, H_2O, MeOH, reflux (85%); (iii) $SOCl_2$, toluene, reflux; (iv) $NH_2OMe{\cdot}HCl$, pyridine, CH_2Cl_2, 0°Crt (79% for **19b**, 80% for **19c**, 68% for **19d**, 82% for **19e**); (v) PIFA, $BF_3{\cdot}OEt_2$ or TFA, CH_2Cl_2, −40−20°C (90% for **20b**, 97% for **20c**, 61% for **20d**, 63% for **20e**).

Transformation of esters **17b**–**e** into the required methoxyamides **19b**–**d** could not be achieved directly following previously reported procedures.[28] Therefore (see Scheme 9), esters **17** were first hydrolyzed under basic or acidic[29] conditions to afford the corresponding carboxylic acids **18b**–**e** which, by previous activation as carbonyl chlorides, were successfully transformed into the desired amides **19b**–**d** in good overall yields (59–70%, three steps). Finally, application of the cyclization conditions on the so-obtained amides **19** resulted in the formation of the target quinolinone-fused heterocycles **20b**–**d**. This final step had to be optimized with respect to the employed activating agent. In fact, it was observed that, whereas no difference was observed in the formation of quinolinone **20e** by using either $BF_3{\cdot}OEt_2$ or TFA (61 vs. 60% yield), boron trifluoride was the reagent of choice in the formation of quinolinones **20b** (90 vs. 75% yield) and **20c** (97 vs. 90% yield). Conversely, TFA afforded a better result in the formation of quinolinone **20d** (61 vs. 40% yield).

3. Conclusion

In summary, new synthetic uses of the hypervalent iodine reagent PIFA for the construction of a series of *N*, *O*, *S*-containing heterocycle-fused quinolinones in a general and efficient way starting from a common β-ketoester precursor **21** has been presented. Our investigations provide preparative approaches to interesting new and complex heterocyclic compounds with potential pharmacological activity.

4. Experimental[30]

Melting points were measured in a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer R-1420 infrared spectrophotometer as KBr plates or as neat liquids and peaks are reported in cm^{-1}. NMR spectra were recorded on a Bruker ACE-250 instrument (250 MHz for ^1H and 62.83 MHz for ^{13}C). Chemical shifts (δ) were measured in ppm relative to chloroform (δ 7.26 for ^1H or 77.00 for ^{13}C) as internal standard; dimethylsulfoxide-d_6 (2.49 for ^1H or 39.5 for ^{13}C) has been used when indicated. Coupling constants, *J*, are reported in Hertz. DEPT experiments were used to assist with the assignation of the signals. Combustion analyses were performed on a Perkin–Elmer 2400 CHN apparatus, and HRMS spectra were recorded at the University of Vigo on a VG Autospec M instrument.

4.1. Typical procedure for the synthesis of amines 6a–c

4.1.1. Synthesis of *N*-(3,4-dimethoxyphenyl)-*N*-[(2-thienyl)methyl]amine (6a). A suspension of 2-thiophenecarboxaldehyde (**5**) (1.0 g, 8.8 mmol) and 3,4-dimethoxyaniline (**4a**) (1.5 g, 9.7 mmol) in toluene (30 mL) was heated at reflux in the presence of 4 Å molecular sieves for 12 h under argon. Then, the mixture was allowed to rise to rt, the solids were filtered, and the solvent was distilled under vacuum. The so-obtained oil was dissolved in MeOH (30 mL), $NaBH_4$ (2.0 g, 52.5 mmol) was added in three portions at 0°C, and the mixture was stirred at rt until total conversion of the starting material. Water (20 mL) was added, the solution was extracted with CH_2Cl_2 (3×20 mL) and dried over sodium sulfate. After evaporation of the solvent, the resulting solid was crystallized from MeOH to afford amine **6a** as a pale brown solid (92%). Mp 56–57°C (MeOH); ^1H NMR ($CDCl_3$), 3.81 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.47 (s, 2H, CH_2), 6.22 (dd, *J*=8.4, 2.3 Hz, 1H, H_{arom}), 6.31 (d, *J*=2.3 Hz, 1H, H_{arom}), 6.75 (d, *J*=8.4 Hz, 1H, H_{arom}), 6.94–7.00 (m, 2H, H_{arom}), 7.22 (d, *J*=4.8 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 43.2, 54.6, 55.6, 98.5, 102.8, 112.4, 123.5, 123.9, 125.9, 140.8, 141.9, 142.8, 149.0. Anal. calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.33; H, 5.99; N, 5.40.

4.1.2. *N*-(3,4-Dimethoxybenzyl)-*N*-[(2-thienyl)methyl]-amine (6b). According to the typical procedure amine **6b** was obtained from benzylamine **4b** in 95% yield as an orange oil. ^1H NMR ($CDCl_3$), 1.66 (br s, 1H, NH), 3.78 (s, 2H, CH_2), 3.87 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.99 (s, 2H, CH_2), 6.80–6.88 (m, 2H, H_{arom}), 6.91–6.98 (m, 3H, H_{arom}), 7.22 (dd, *J*=5.0, 1.4 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 46.7, 51.7, 55.0, 55.1, 110.2, 110.6, 119.5, 123.6, 124.1, 125.9, 132.0, 143.7, 147.3, 148.2; HRMS calcd for $C_{14}H_{17}NO_2S$ 263.0980, found 263.0980.

4.1.3. *N*-(3,4-Dimethoxyphenethyl)-*N*-[(2-thienyl)methyl]-amine (6c). According to the typical procedure amine **6c** was obtained from phenethylamine **4c** in 90% yield as an orange oil. ^{1}H NMR ($CDCl_3$), 1.53 (br s, 1H, NH), 2.77 (t, J=6.6 Hz, 2H, CH_2), 2.91 (t, J=6.6 Hz, 2H, CH_2), 3.85 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.99 (s, 2H, CH_2), 6.72–6.81 (m, 3H, H_{arom}), 6.89–6.95 (m, 2H, H_{arom}), 7.20 (dd, J=5.0, 1.0 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 34.6, 47.1, 49.3, 54.4, 54.5, 110.2, 110.9, 119.4, 123.0, 123.4, 125.3, 131.4, 143.3, 146.2, 147.7; HRMS calcd for $C_{15}H_{19}NO_2S$ 277.1137, found 277.1142.

4.2. Typical procedure for the synthesis of *N*-trifluoroacetamides 7a–c

4.2.1. Synthesis of *N*-(3,4-dimethoxyphenyl)-*N*-[(2-thienyl)methyl]-trifluoroacetamide (7a). Trifluoroacetic anhydride (2.8 mL, 20.1 mmol) was added to a solution of amine **6a** (2.0 g, 8.0 mmol) in pyridine (20 mL) at 0°C, and the mixture was stirred for 1 h. Then, water (20 mL) and EtOAc (20 mL) was added and the mixture was washed with 5% aq HCl (1×20 mL), water (1×20 mL), brine (1×20 mL), and the organic phase was dried over sodium sulfate. After distillation of the solvent, the resulting solid was crystallized from hexanes to afford amide **7a** as a pale brown solid (70% yield). Mp 53–55°C (hexanes); ^{1}H NMR ($CDCl_3$), 3.75 (s, 3H, OMe), 3.88 (s, 3H, OMe), 5.00 (br s, 2H, CH_2), 6.51 (d, J=1.6 Hz, 1H, H_{arom}), 6.66 (dd, J=8.3, 1.6 Hz, 1H, H_{arom}), 6.80–6.93 (m, 3H, H_{arom}), 7.27 (d, J=5.2 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 49.4, 55.3, 55.4, 110.2, 111.1, 116.0 (q, J=289 Hz), 120.4, 126.1, 126.2, 128.3, 130.5, 136.6, 148.5, 149.1, 156.2 (q, J=36 Hz); IR (neat) 1694. Anal. calcd for $C_{15}H_{14}F_3NO_3S$: C, 52.17; H, 4.09; N, 4.06. Found: C, 52.26; H, 4.33; N, 4.12.

4.2.2. *N*-(3,4-Dimethoxybenzyl)-*N*-[(2-thienyl)methyl]-trifluoroacetamide (7b). According to the typical procedure amide **7b** was obtained from amine **6b** in 75% yield (rotamer mixture 46:54) as an orange oil. ^{1}H NMR ($CDCl_3$), 3.85 (s, 3H, OMe), 3.88 and 3.89 (s, total 3H, OMe), 4.53 (s, 2H, CH_2), 4.62 (s, 2H, CH_2), 6.71–7.02 (m, 5H, H_{arom}), 7.33 (d, J=5.2 Hz) and 7.26 (d, J=5.2 Hz, total 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 42.5, 43.7, 47.1, 48.9, 55.2, 110.0, 110.6, 110.8, 111.0, 116.2 (q, J=288 Hz), 119.9, 120.6, 125.8, 126.0, 126.2, 127.2, 127.5, 136.5, 148.4, 148.6, 148.8, 149.0, 156.1 (q, J=36 Hz), 156.3 (q, J=36 Hz); IR (neat) 1690; HRMS calcd for $C_{16}H_{16}NO_3F_3S$ 359.0803, found 359.0806.

4.2.3. *N*-(3,4-Dimethoxyphenethyl)-*N*-[(2-thienyl)-methyl]-trifluoroacetamide (7c). According to the typical procedure amide **7c** was obtained from amine **4c** in 80% yield (rotamer mixture 50:50) as an orange oil. ^{1}H NMR ($CDCl_3$), 2.74–2.89 (m, 2H, CH_2), 3.52–3.61 (m, 2H, CH_2), 3.86 (s, 6H, OMe), 4.48 and 4.73 (s, total 2H, CH_2), 6.65–6.72 (m, 2H, H_{arom}), 6.80–6.83 (m, 1H, H_{arom}), 6.92–7.00 (m, 2H, H_{arom}), 7.28–7.31 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 31.6, 34.0, 44.0, 45.7, 47.5, 47.7, 54.9, 110.7, 110.8, 111.1, 111.2, 115.9 (q, J=289 Hz), 120.0, 125.6, 125.7, 126.0, 126.3, 126.9, 127.0, 129.1, 130.0, 136.6, 136.8, 147.1, 147.3, 148.3, 148.4, 155.3 (q, J=36 Hz), 156.1 (q, J=36 Hz); IR (neat) 1690; HRMS calcd for $C_{17}H_{18}F_3NO_3S$ 373.0957, found 373.0959.

4.2.4. 8,9-(Dimethoxy)-5-trifluoroacetyl-5,6-dihydro-4*H*-thieno[2,3-*d*][2]benzoazepine (8b). A solution of PIFA (270 mg, 0.63 mmol) and $BF_3{\cdot}OEt_2$ (0.10 mL, 0.83 mmol) in CH_2Cl_2 (13 mL) was added to a solution of amide **7b** (150 mg, 0.42 mmol) in 8.5 mL of the same solvent. After 1 h, the solvent was removed in vacuo and the residue was subjected to flash chromatography (hexanes/EtOAc, 7:3) to yield benzoazepine **8b** (47%) as an oil which was crystallized from hexanes (rotamer mixture 62:38). Mp 119–121°C (hexanes); ^{1}H NMR ($CDCl_3$), 3.94 (s, 6H, OMe), 4.42 and 4.49 (s, total 2H, CH_2), 4.60 and 4.64 (s, total 2H, CH_2), 6.88 and 6.98 (s, total 1H, H_{arom}), 7.02 (s, 1H, H_{arom}), 7.25 (d, J=5.2 Hz, 1H, H_{arom}), 7.35 (d, J=5.2 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 43.5, 48.4, 56.0, 110.0, 110.2, 112.2, 113.6, 116.5 (q, J=287 Hz), 116.6 (q, J=287 Hz), 124.9, 125.1, 125.6, 127.2, 127.4, 128.8, 129.0, 130.1, 130.5, 141.0, 141.2, 148.4, 148.5, 149.2, 149.4, 155.0 (q, J=36 Hz), 155.2 (q, J=36 Hz); IR (KBr) 1685. Anal. calcd for $C_{16}H_{14}F_3NO_3S$: C, 53.78; H, 3.95; N, 3.92. Found: C, 53.66; H, 3.79; N, 3.82.

4.2.5. 9,10-(Dimethoxy)-5-trifluoroacetyl-4,5,6,7-tetrahydrothieno[2,3-*e*][3]benzoazocine (8c). A solution of PIFA (175 mg, 0.40 mmol) and $BF_3{\cdot}OEt_2$ (0.07 mL, 0.54 mmol) in CH_2Cl_2 (25 mL) was added to a solution of amide **7c** (100 mg, 0.27 mmol) in 8.5 mL of the same solvent at −40°C. After 12 h, the solvent was removed in vacuo and the residue was subjected to flash chromatography (hexanes/EtOAc, 7:3) yielding the benzoazocine **8c** in 20% yield as an oil which was crystallized from hexanes. Mp 148–150°C (hexanes); ^{1}H NMR ($CDCl_3$), 2.37–2.42 (m, 1H, H-7), 2.99–3.07 (m, 1H, H-7), 3.22–3.27 (m, 1H, H-6), 3.56 (d, J=14.3 Hz, 1H, H-4), 3.89 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.24–4.32 (m, 1H, H-6), 5.22 (d, J=14.3 Hz, 1H, H-4), 6.76 (s, 1H, H_{arom}), 6.85 (s, 1H, H_{arom}), 7.05 (d, J=5.2 Hz, 1H, H_{arom}), 7.30 (d, J=5.2 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 35.2, 44.1, 48.4, 48.5, 55.9, 111.9, 112.6, 116.3 (q, J=287 Hz), 125.3 127.4, 127.9, 130.7, 131.8, 140.5, 147.5, 148.8, 155.7 (q, J=36 Hz); IR (KBr) 1688. Anal. calcd for $C_{17}H_{16}F_3NO_3S$: C, 54.98; H, 4.34; N, 3.77. Found: C, 55.00; H, 4.59; N, 3.88.

4.3. Typical procedure for the synthesis of amides 10a–c

4.3.1. Synthesis of *N*-(3,4-dimethoxyphenyl)-2-thiophene-carboxamide (10a). Pyridine (1.3 mL, 16.3 mmol) was added to a solution of commercially available 2-thiophenecarbonyl chloride (**9**) (1.0 g, 6.8 mmol) and amine **4a** (1.91 g, 3.80 mmol) in CH_2Cl_2 (30 mL) at 0°C, and the mixture was stirred at rt until total consumption of the starting material (tlc, Hex/EtOAc, 1:1, 12 h). Then, the crude mixture was washed with a saturated solution of $CuSO_4$ (3×10 mL) and water (2×10 mL). The organic phase was dried over sodium sulfate and the solvent was distilled under vacuum to afford amide **10a** as a white solid which was purified by crystallization from MeOH (94% yield). Mp 175–177°C (MeOH); ^{1}H NMR (DMSO-d_6), 3.73 (s, 3H, OMe), 3.75 (s, 3H, OMe), 6.93 (d, J=8.8 Hz, 1H, H_{arom}), 7.19–7.23 (m, 1H, H_{arom}), 7.27 (dd, J=8.8, 2.3 Hz, 1H, H_{arom}), 7.39 (d, J=2.3 Hz, 1H, H_{arom}), 7.83 (d, J=4.6 Hz, 1H, H_{arom}), 7.98 (d, J=3.8 Hz, 1H, H_{arom}), 10.1 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6), 55.4, 55.7, 105.5, 111.9, 112.5, 128.2, 128.8, 131.7, 132.3, 140.4, 145.3, 148.5, 159.7; IR

(KBr) 1633. Anal. calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.26; H, 4.73; N, 5.22.

4.3.2. *N*-(3,4-Dimethoxybenzyl)-2-thiophenecarboxamide (10b). According to the typical procedure amide **10b** was obtained from benzylamine **4b** in 72% yield as a white solid. Mp 118–119°C (MeOH); ^{1}H NMR ($CDCl_3$), 3.65 (s, 3H, OMe), 3.71 (s, 3H, OMe), 4.39 (d, J=5.6 Hz, 2H, CH_2), 6.62–6.76 (m, 3H, H_{arom}), 6.92 (dd, J=4.8, 3.9 Hz, 1H, H_{arom}), 7.37 (d, J=4.8 Hz, 1H, H_{arom}), 7.56 (t, J=5.6 Hz, 1H, NH), 7.61 (d, J=3.9 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 43.4, 55.4, 55.5, 110.7, 110.8, 119.9, 127.4, 127.9, 129.9, 130.5, 138.8, 148.0, 148.6, 161.8; IR (KBr) 1629. Anal. calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.36; H, 5.53; N, 5.32.

4.3.3. *N*-(3,4-Dimethoxyphenethyl)-2-thiophenecarboxamide (10c). According to the typical procedure amide **10c** was obtained from phenethylamine **4c** in 97% yield as a yellowish solid. Mp 95–97°C (hexanes); ^{1}H NMR ($CDCl_3$), 2.87 (t, J=6.7 Hz, 2H, CH_2), 3.62–3.70 (m, 2H, CH_2), 3.84 (s, 3H, OMe), 3.87 (s, 3H, OMe), 6.04 (br s, 1H, NH), 6.74–6.84 (m, 3H, H_{arom}), 7.05 (dd, J=5.0, 4.0 Hz, 1H, H_{arom}), 7.41 (d, J=4.0 Hz, 1H, H_{arom}), 7.45 (d, J=5.0 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 34.9, 41.2, 55.3, 55.4, 110.9, 111.5, 120.3, 127.3, 127.7, 129.7, 131.1, 138.9, 147.1, 148.4, 161.9; IR (KBr) 1628. Anal. calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.63; H, 5.70; N, 4.62.

4.4. Typical procedure for the synthesis of *N*-methylamides 11a–c

4.4.1. Synthesis of *N*-(3,4-dimethoxyphenyl)-*N*-methyl-2-thiophenecarboxamide (11a). A solution of MeI (1.9 mL, 30.4 mmol) and amide **10a** in THF (60 mL) was added to a suspension of NaH (228 mg, 9.5 mmol) in 15 mL of the same solvent at 0°C. After stirring for 20 min, temperature was raised to rt and stirring was continued during 3 h. Then, water (60 mL) was added, decanted, and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic extracts were dried over sodium sulfate and the solvent was distilled under vacuum. The resulting residue was crystallized from hexanes to afford amide **11a** as a pale brown powder (96% yield). Mp 120–122°C (hexanes); ^{1}H NMR ($CDCl_3$), 3.42 (s, 3H, NMe), 3.82 (s, 3H, OMe), 3.92 (s, 3H, OMe), 6.74 (d, J=2.0 Hz, 1H, H_{arom}), 6.79–6.88 (m, 4H, H_{arom}), 7.30 (dd, J=4.8, 1.2 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 38.9, 55.7, 55.8, 111.0, 120.1, 126.4, 130.4, 131.9, 136.6, 137.7, 148.6, 149.3, 162.3; IR (KBr) 1624. Anal. calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.36; H, 5.74; N, 5.19.

4.4.2. *N*-(3,4-Dimethoxybenzyl)-*N*-methyl-2-thiophenecarboxamide (11b). According to the typical procedure amide **11b** was obtained from amide **10b** in 84% yield as an orange oil. ^{1}H NMR ($CDCl_3$ at 42°C), 3.10 (s, 3H, NMe), 3.86 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.70 (s, 2H, CH_2), 6.82–6.88 (m, 3H, H_{arom}), 6.99–7.03 (m, 1H, H_{arom}), 7.34 (d, J=3.6 Hz, 1H, H_{arom}), 7.43 (d, J=4.8 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 35.2, 52.8, 55.7, 110.9, 111.5, 119.6, 126.4, 128.5, 129.1, 137.6, 148.4, 149.2, 164.2; IR (neat) 1617; HRMS calcd for $C_{15}H_{17}NO_3S$ 291.0929, found 291.0930.

4.4.3. *N*-(3,4-Dimethoxyphenethyl)-*N*-methyl-2-thiophenecarboxamide (11c). According to the typical procedure amide **11c** was obtained from amide **10c** in 90% yield as a brownish oil. ^{1}H NMR ($CDCl_3$ at 42°C), 2.88 (t, J=7.3 Hz, 2H, CH_2), 3.10 (s, 3H, NMe), 3.73 (t, J=7.3 Hz, 2H, CH_2), 3.82 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.70–6.81 (m, 3H, H_{arom}), 7.00 (dd, J=5.2, 4.0 Hz, 1H, H_{arom}), 7.24 (d, J=4.0 Hz, 1H, H_{arom}), 7.40 (dd, J=5.2, 1.2 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 32.9, 35.8, 51.0, 55.2, 55.3, 111.4, 112.0, 120.2, 125.9, 127.7, 128.0, 130.6, 137.4, 147.3, 148.6, 163.4; IR (neat) 1615; HRMS calcd for $C_{16}H_{19}NO_3S$ 305.1085, found 305.1096.

4.4.4. Ethyl 2-(*N*,*N*-dimethylaminomethyliden)benzoylacetate (23). DMFDMA (0.9 mL, 6.37 mmol) was added dropwise to a solution of commercially available ketoester **21** (1.0 g, 5.78 mmol) in 7 mL of toluene, and the mixture was stirred at 60°C for 24 h. After cooling, solvent was evaporated in vacuo, and the resulting oil was column chromatographed (hexanes/EtOAc, 6:4) to afford ester **23** which was crystallized from hexanes (92%) as a yellowish solid. Mp 26–29°C (hexanes); ^{1}H NMR ($CDCl_3$), 0.91 (t, J=7.1 Hz, 3H, CMe), 3.01 (br s, 6H, NMe_2), 3.98 (q, J=7.1 Hz, 2H, CH_2), 7.38–7.48 (m, 3H, H_{arom}), 7.57–7.81 (m, 3H, H–C=, H_{arom}); ^{13}C NMR ($CDCl_3$), 13.5, 41.0, 45.5, 59.2, 99.1, 127.5, 128.4, 131.2, 140.6, 155.5, 168.2, 193.6; IR (KBr) 1684, 1631; HRMS calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1203.

4.4.5. 1-Phenylbut-2-yn-1-one (16).[19] 1-Propynylmagnesium bromide (**14**) (20.8 mL, 0.5 M in THF, 10.4 mmol) was added to a solution of benzaldehyde (**13**) (1 g, 9.4 mmol) in 50 mL of THF at 0°C. The mixture was stirred at the same temperature until the conversion was complete (NMR, 90 min). Then, a saturated solution of NH_4Cl (20 mL) was added and the aqueous phase was extracted with EtOAc (3×20 mL). The combined extracts were dried (Na_2SO_4) and evaporated to yield alcohol **15**. Without isolation, crude alcohol **15** was dissolved in 10 mL of CH_2Cl_2 and added to a suspension of MnO_2 (28.2 g, 324 mmol) in CH_2Cl_2 (25 mL). The mixture was stirred for 1 h at 0°C, filtered through a pad of celite and $MgSO_4$, and concentrated in vacuo to yield ketone **16** (92%, two steps).

4.4.6. 2-Methoxycarbonyl-5-methyl-3-phenylthiophene (17a). Methyl thioglycolate (0.74 mL, 8.3 mmol) was added over a cold (0°C) solution of crude ketone **16** (1.2 g, 8.3 mmol) in 30 mL of THF. After stirring for 2 h, MeOH (8.3 mL) and Cs_2CO_3/$MgSO_4$ (8.3 g, 1:2) were added and stirring was continued for 15 min at the same temperature and for 2 h at rt. Then, the mixture was poured onto an ice-cooled 2N aq NaH_2PO_4 solution (150 mL) and EtOAc. The aqueous phase was extracted with EtOAc (3×25 mL). The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to afford ester **17a** as an oil that was crystallized from hexanes (97%). Mp 95–97°C (hexanes); ^{1}H NMR ($CDCl_3$), 2.52 (s, 3H, Me), 3.74 (s, 3H, OMe), 6.78 (s, 1H, H-4), 7.37–7.43 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$), 15.3, 51.4, 123.8, 127.4, 127.5, 128.9, 130.1, 135.6, 145.1, 148.8, 162.1; IR (KBr) 1718. Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found: C, 67.41; H, 5.44.

4.4.7. 2-Carboxy-5-methyl-3-phenylthiophene (18a). Sodium hydroxide (12.0 g, 310 mmol) was added to a solution of ester **17a** (1.8 g, 7.8 mmol) in 40 mL of a mixture of MeOH/THF/H_2O (6.5:2.0:1.5) and the mixture was stirred until total consumption of the starting material. Then, the solution was treated with HCl (5% aq) and extracted with EtOAc (3×20 mL). The organic extracts were dried over sodium sulfate and the solvent was evaporated under reduced pressure to afford carboxylic acid **18a** as an oil that was crystallized from Et_2O (97%). Mp 181–182°C (Et_2O); ^{1}H NMR (MeOH-d_4), 2.47 (s, 3H, Me), 6.77 (s, 1H, H-4), 7.28–7.36 (m, 5H, H_{arom}); ^{13}C NMR (DMSO-d_6), 15.4, 126.2, 128.6, 128.7, 130.2, 131.6, 137.4, 146.8, 150.3, 165.1; IR (KBr) 1677. Anal. calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62. Found: C, 66.33; H, 4.40.

4.5. Typical procedure for the synthesis of amides 19

4.5.1. Synthesis of *N*-methoxycarbamoyl-5-methyl-3-phenylthiophene (19a). Thionyl chloride (0.86 mL, 11.7 mmol) was added to a solution of acid **18a** (1.7 g, 7.8 mmol) in 60 mL of toluene and the mixture was heated to reflux for 4 h. Then, the mixture was cooled to rt and the solvent was evaporated under reduced pressure. The so-obtained oil was dissolved in 60 mL of CH_2Cl_2 and NH_2OMe·HCl (716 mg, 8.6 mmol) and pyridine (1.26 mL, 15.6 mmol) were added. The new mixture was stirred at rt until total consumption of the starting material (^{1}H NMR). Then, the solution was treated with a saturated aqueous solution of $CuSO_4$ (3×20 mL). The organic phase was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The resulting residue was column chromatographed (Hex/EtOAc, 7:3) to afford amide **19a** as an oil which was crystallized from Et_2O as a white powder (65%). Mp 102–104°C (Et_2O); ^{1}H NMR ($CDCl_3$), 2.50 (s, 3H, Me), 3.66 (s, 3H, OMe), 6.70 (s, 1H, H-4), 7.38–7.45 (m, 5H, H_{arom}), 7.98 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$), 15.2, 64.0, 127.8, 128.3, 128.5, 128.7, 128.9, 135.2, 142.9, 144.1, 161.1; IR (KBr) 3189, 1649. Anal. calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.33; H, 5.15; N, 5.29.

4.5.2. 4-(*N*-Methoxycarbamoyl)-5-phenylisoxazole (19d). According to the typical procedure amide **19d** was obtained from acid **18d**[31] in 68% yield as a pale brown solid. Mp 109–111°C (Et_2O); ^{1}H NMR ($CDCl_3$), 3.69 (s, 3H, OMe), 7.39–7.43 (m, 3H, H_{arom}), 7.84–7.87 (m, 2H, H_{arom}), 8.52 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$), 64.2, 108.3, 125.9, 128.2, 128.7, 131.4, 149.8, 159.8, 169.9; IR (KBr) 3201, 1655. Anal. calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.65; H, 4.69; N, 13.01.

4.5.3. 1,5-Diphenyl-4-(*N*-methoxycarbamoyl)pyrazole (19e). According to the typical procedure pyrazole **19e** was obtained from ester **18e**[32] in 82% yield as a pale brown solid. Mp 173–175°C (hexanes); ^{1}H NMR ($CDCl_3$), 3.67 (s, 3H, OMe), 7.14–7.38 (m, 10H, H_{arom}), 8.11 (s, 1H, H-3), 8.56 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$), 64.3, 114.6, 125.0, 127.9, 128.4, 128.7, 128.8, 129.7, 130.1, 138.8, 140.8, 142.1, 161.7; IR (KBr) 3236, 1643. Anal. calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.66; H, 5.39; N, 14.40.

4.6. Typical procedure for the synthesis quinolinones 20a–e

4.6.1. Synthesis of *N*-methoxy-2-methylthieno[2,3-*c*]-quinolin-4-one (20a). A solution of PIFA (1.03 mmol) and the activating agent (BF_3·OEt_2 for **20a**–**c** and TFA for **20d**,**e**, 3.0 mmol) in 15 mL of CH_2Cl_2 was added at 0°C (at −20°C for **20b**–**e**) to a solution of amide **19a** (1.0 mmol) in 10 mL of the same solvent. The mixture was stirred at the same temperature during 1 h and then treated with Na_2CO_3 (aq), decanted and dried over sodium sulfate. The oil obtained after solvent evaporation was column chromatographed (Hex/EtOAc, 3:7) and crystallized from hexanes to afford quinolinone **20a** as a pale brown solid in 91% yield. Mp 130–132°C (hexanes); ^{1}H NMR ($CDCl_3$), 2.67 (s, 3H, Me), 4.14 (s, 3H, NOMe), 7.29–7.36 (m, 1H, H_{arom}), 7.40 (s, 1H, H-1), 7.54–7.60 (m, 1H, H_{arom}), 7.69 (d, J=8.3 Hz, 1H, H_{arom}), 7.92 (d, J=7.9 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 16.3, 63.0, 112.7, 117.0, 120.4, 122.8, 124.2, 128.6, 129.2, 136.2, 141.7, 149.1, 153.7; IR (KBr) 1656. Anal. calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.73; H, 4.44; N, 5.65.

4.6.2. *N*-Methoxy-2-methylthiazolo[5,4-*c*]quinolin-4-one (20b). According to the typical procedure, quinolinone **20b** was obtained from amide **19b**[13] in 90% yield as a brown solid. Mp 184–186°C (hexanes); ^{1}H NMR ($CDCl_3$), 2.91 (s, 3H, Me), 4.15 (s, 3H, OMe), 7.37–7.44 (m, 1H, H_{arom}), 7.62–7.73 (m, 2H, H_{arom}), 8.40–8.43 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 20.2, 63.2, 112.4, 116.5, 123.3, 124.7, 130.4, 136.6, 153.5, 154.4, 173.6; IR (KBr) 1656. Anal. calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.37. Found: C, 58.73; H, 4.10; N, 11.15.

4.6.3. *N*-Methoxy-2-phenylthiazolo[5,4-*c*]quinolin-4-one (20c). According to the typical procedure, quinolinone **20c** was obtained from amide **19c**[13] in 97% yield as a white solid. Mp 183–185°C (Et_2O); ^{1}H NMR ($CDCl_3$), 4.19 (s, 3H, OMe), 7.43 (t, J=7.9 Hz, 1H, H_{arom}), 7.53–7.55 (m, 3H, H_{arom}), 7.64–7.75 (m, 2H, H_{arom}), 8.14–8.17 (m, 2H, H_{arom}), 8.56 (d, J=7.9 Hz, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$), 63.2, 112.3, 116.6, 123.2, 124.5, 124.8, 127.2, 128.9, 130.3, 131.5, 132.5, 136.6, 153.5, 155.0, 174.0; IR (KBr) 1668. Anal. calcd for $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08. Found: C, 66.33; H, 3.79; N, 9.10.

4.6.4. *N*-Methoxyisoxazolo[4,5-*c*]quinolin-4-one (20d). According to the typical procedure quinolinone **20d** was obtained from amide **19d** in 61% yield as a white. Mp>200°C (hexanes); ^{1}H NMR ($CDCl_3$), 4.12 (s, 3H, OMe), 7.39–7.45 (m, 1H, H_{arom}), 7.69–7.76 (m, 2H, H_{arom}), 8.10–8.13 (m, 1H, H_{arom}), 8.92 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$), 63.4, 108.7, 110.4, 113.2, 123.4, 123.7, 133.1, 137.4, 147.4, 153.3, 165.6; IR (KBr) 1684. Anal. calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.23; H, 3.69; N, 13.00.

4.6.5. *N*-Methoxy-1-phenylpyrazolo[4,5-*c*]quinolin-4-one (20e). According to the typical procedure, quinolinone **20e** was obtained from amide **19e** in 63% yield as a white solid. Mp 192–194°C (hexanes); ^{1}H NMR ($CDCl_3$), 4.10 (s, 3H, OMe), 6.98–7.22 (m, 2H, H_{arom}), 7.50–7.69 (m, 7H, H_{arom}), 8.41 (s, 1H, H-3); ^{13}C NMR ($CDCl_3$), 62.8, 110.2,

113.1, 113.8, 122.4, 122.8, 126.8, 129.7, 129.9, 130.3, 136.5, 138.2, 138.6, 139.8, 154.1; IR (KBr) 1678. Anal. calcd for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 70.22; H, 4.39; N, 14.20.

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