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An advantageous synthesis of new indazolone and pyrazolone derivatives

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Abstract—The synthesis of new indazolone and pyrazolone derivatives starting from methyl anthranilate type substrates is presented. This general approach constitutes a novel and advantageous alternative for the synthesis of the target heterocycles, which implies the use of the environmentally friendly oxidizer PIFA. The synthetic design includes the oxidation of *N*-arylamides by the hypervalent iodine reagent to the corresponding *N*-acylnitrenium ions, which can be intramolecularly trapped by an amine moiety to furnish the title compounds by formation of a new N–N single bond.

1. Introduction

In spite of the limited occurrence of the indazole skeleton as a structural motif in natural products—to the best of our knowledge *nigellicine*[1] and *nigellidine*[2] (see Fig. 1) are the only examples found in the literature—an intensive effort for the development of efficient synthetic routes toward the preparation of these types of alkaloids has been carried out. This interest is mainly fueled by the promising pharmaceutical activities that they show. In fact, since benzydamine, the first non-steroidal anti-inflammatory drug (NSAID) bearing an indazole subunit, was commercialized in 1960,[3] many reports on the anti-inflammatory,[4] antipyretic,[5] analgesic,[6] and antihyperlipidemic[7] properties of these kinds of compounds, particularly of indazol-3-one derivatives, have appeared in the literature. Additionally, other simplified related structures, such as pyrazolones, have recently caught the attention of the medicinal community because of their bioactivity as inhibitors of tumor necrosis factor-α (TNF-α) production.[8] Nevertheless, despite the existence of a wide range of routes for the synthesis of the target heterocycles, an examination of the literature reveals that the chemistry involved in their preparation often lacks useful generality, entails certain inconvenient reagents, and implies, in some cases, the use of either expensive reagents or starting materials.[9]

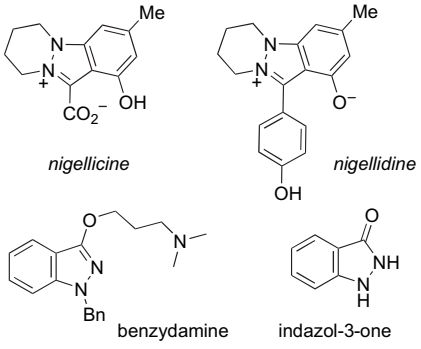

Figure 1. Selected examples of indazole derivatives.

One of our ongoing research lines deals with the search for novel applications of the hypervalent iodine reagent PIFA [phenyliodine(III)bis-(trifluoroacetate)] in heterocyclic synthesis,[10] a tactic that has found efficient applications in the synthesis of a number of compounds, which might be appealing for medicinal purposes.[11] Among them, we have recently reported an alternative access to the indazolone skeleton **1** through a PIFA-mediated oxidative cyclization.[12] This novel approach, disclosed in Scheme 1, is based on the ability of PIFA to oxidize adequately substituted amides to the corresponding *N*-acylnitrenium intermediates.[13] Then, in the presence of an amine moiety, an intramolecular attack leads to the construction of new N–N linkages affording the desired heterocycle.

In our preliminary communication we were intrigued by both the best experimental conditions to carry out the reaction, and the structural requirements of the substrates for an efficient transformation. This optimization process led to the conclusion that the cyclization protocol was restricted to aromatic amides and substituted nucleophilic amines, a result that is coherent with the mechanistic proposal shown

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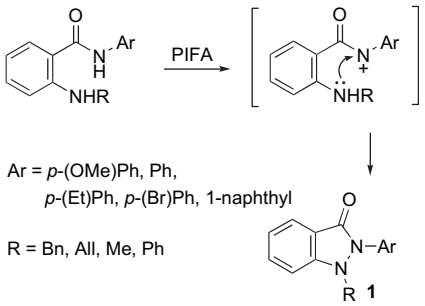
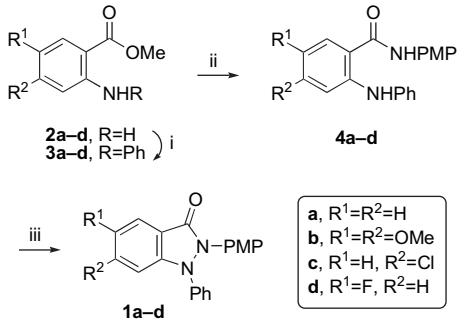


Scheme 1. Designed strategy for the synthesis of indazolones of type **1**.

above for this transformation. Additionally, the multiple and interesting pharmacological activities that these derivatives can display suggest that additional bioactivities are likely to be found when similar systems are tested. Now, in this paper, the success of the described methodology for the synthesis of related structures will be examined. Thus, herein we would like to report the application of the PIFA-mediated N–N bond forming process to the synthesis of a series of indazolone derivatives in which the benzo-moiety is replaced by other motifs, such as either substituted arene rings or the heterocyclic thiophene system. In addition, the construction of the pyrazolone nucleus, which is present in important groups of therapeutic agents, is also reported following this protocol.

2. Results and discussion

Once the *para*-methoxyphenyl group (PMP) had been selected as the proper neighboring group to stabilize the corresponding *N*-acylnitrenium ions,[14] and the phenyl group as an adequate substituent to make the amine functionality nucleophilic enough to attack such intermediates, a series of substrates **4a–d** were chosen to construct the target indazolone derivatives. These precursors were obtained (see Scheme 2) in a two-step synthesis from commercially available methyl anthranilates **2a–d** by a palladium-catalyzed *N*-arylation reaction using bromobenzene as the arylating agent,[15] followed by the direct transformation of the resulting aminoesters **3a–d** into the desired amides **4a–d** by a $AlMe_3$-mediated aminolysis reaction.[16] Next, we studied the behavior of these aromatic amides with the trivalent iodine reagent PIFA under the cyclization conditions previously optimized by our research group.[12]



Scheme 2. Reagents and conditions: (i) PhBr, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 100 °C, sealed tube; (ii) $AlMe_3$, *para*-anisidine, CH_2Cl_2, reflux; (iii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 °C.

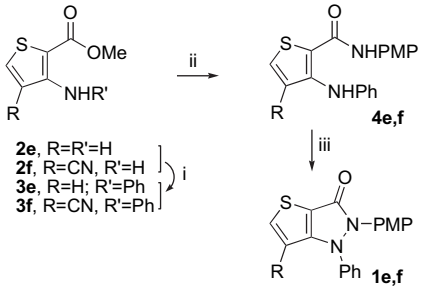
Table 1. Synthetic details for the transformation of **2a–d** to **1a–d**

Entry	**3a–d** (%)[a]	**4a–d** (%)[b]	**1a–d** (%)[a]
1	**3a** (93)	**4a** (69)	**1a** (61)
2	**3b** (85)	**4b** (68)	**1b** (0)
3	**3c** (71)	**4c** (70)	**1c** (81)
4	**3d** (85)	**4d** (70)	**1d** (77)

[a] Isolated yields after purification by flash-chromatography.
[b] Isolated yields after purification by crystallization from Et_2O.

As shown in Table 1, the success of the proposed PIFA-mediated cyclization process revealed a strong dependence on the nature of the substituents in the aryl ring. Thus, it proved to be suitable for unsubstituted substrates (entry 1) and for substrates bearing electron-withdrawing groups such as chlorine (entry 3) and fluorine (entry 4) affording the desired indazolones **1a**, **1c**, and **1d** in 61, 81, and 77% yields, respectively. In contrast, the cyclization process failed when it was tested on the dimethoxy-substituted amide **4b** (entry 2). In this case, the desired indazolone **1b** was not even detected, and a complex mixture of products was obtained instead. Therefore, these results suggest that the required PIFA-promoted oxidation of the amide functionality is precluded with respect to an oxidation process that would take place on highly enriched aromatic rings (i.e., **4b**) failing, hence, to afford the desired heterocycle.

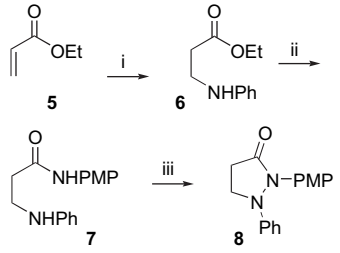
As mentioned above, in order to investigate the extension of the presented methodology to other fused heterocyclic systems, we also faced the synthesis of the related thieno-fused pyrazolone derivatives **1e**,**f** by a common sequence as shown in Scheme 3. Thus, methyl 3-amino-2-thiophenecarboxylates **2e**,**f** were submitted to a palladium-catalyzed *N*-arylation process affording satisfactorily the corresponding *N*-phenyl derivatives **3e**,**f**, which were next efficiently transformed into the desired aromatic amides **4e**,**f**. On treatment with the hypervalent iodine reagent PIFA, it was observed that even after application of a complete array of experimental conditions (by modifying solvents, temperature, and additives), amide **4e** could never furnish the corresponding bicycle **1e**, and complete degradation of the starting material was observed. Although synthetically discouraging, this result could be anticipated considering the similar electronic nature of the 3,4-dimethoxyphenyl and thienyl systems. For that reason, we also experimented the behavior of amide **4f** under our PIFA-promoted cyclization conditions. In this particular case, the desired



Scheme 3. Reagents and conditions: (i) PhBr, $Pd(OAc)_2$, Xantphos, Cs_2CO_3, toluene, 100 °C, sealed tube (69% for **3e**, 57% for **3f**); (ii) $AlMe_3$, *para*-anisidine, CH_2Cl_2, reflux (82% for **4e**, 68% for **4f**); (iii) PIFA (0.01 M), CH_2Cl_2, TFA, 0 °C (0% for **1e**, 61% for **1f**).

thieno-fused pyrazolone **1f** was obtained in a nice 61% yield. Apparently, the decrease of the oxidation potential of the thiophene ring due to the presence of the electron-withdrawing cyano group allows nitrogen oxidation and, therefore, the cyclization reaction to take place.[17]

Finally, taking into account the already described favorable results, we decided to test the presented oxidative process on a linear amide to determine its suitability for the construction of the simple pyrazolone skeleton. In this case (see Scheme 4) the synthesis of the required *para*-methoxyphenylamide **7** was accomplished by following a known[18] aza-Michael reaction on ethyl acrylate **5**, followed by a $AlMe_3$-promoted amidation protocol on the so-obtained derivative **6**. Next, when amide **7** was submitted to the action of PIFA, the desired pyrazolone derivative **8** was obtained in a moderate 35% yield using trifluoroethanol as solvent, instead of CH_2Cl_2/TFA as for the previous examples, to attain complete conversion of the starting material.



Scheme 4. Reagents and conditions: (i) $PhNH_2$, $FeCl_3 \cdot 7H_2O$, H_2O, room temperature (72%); (ii) $AlMe_3$, *para*-anisidine, CH_2Cl_2, reflux (72%); (iii) PIFA (0.01 M), TFEA, 0 °C (35%).

3. Conclusions

A practical and facile approach to the synthesis of *N*,*N*-disubstituted indazolone and pyrazolone derivatives has been developed. Our method features the succeeding intramolecular trapping of *N*-acylnitrenium ions, which are generated by the oxidative action of PIFA on aromatic amides, by amines functionalities providing, hence, a novel and versatile route for the construction of the title heterocycles through the formation of new N–N linkages under rather mild experimental conditions. Furthermore, a study on the pharmacological activity that these derivatives may exhibit is currently in progress.

4. Experimental

4.1. General

All reagents were purchased and used as received. Melting points were measured using open glass capillaries and are uncorrected. Infrared spectra were recorded as KBr plates or as thin films and peaks are reported in cm^{-1}. Only representative absorptions are given. NMR spectra were recorded on a 300 (300 MHz for ^1H and 75.4 MHz for ^{13}C) instrument at 20 °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. Coupling constants, *J*, are reported in hertz. DEPT experiments were used to assist with the assignation of the signals. HRMS spectra were measured by using a Waters GCT Mass Spectrometer.

4.2. Typical procedure for the Pd-catalyzed *N*-arylation reaction. Preparation of esters 3a–f

4.2.1. Synthesis of methyl *N*-phenylanthranilate (3a). A solution of commercially available methyl anthranilate (**2a**) (0.70 mL, 5.29 mmol), bromobenzene (0.47 mL, 4.41 mmol), $Pd(OAc)_2$ (20.2 mg, 0.09 mmol), Xantphos (104 mg, 0.18 mmol), and Cs_2CO_3 (2.01 g, 6.17 mmol) in toluene (18 mL) was heated at 100 °C in a sealed tube. After 3 h the reaction mixture was filtered and the so-obtained solid residue was washed with CH_2Cl_2 (3×15 mL). Then, the resulting organic layer was concentrated in vacuo and the crude product was purified by flash-chromatography (CH_2Cl_2) to afford the *N*-phenyl derivative **3a** (93%) as yellowish oil.[12]

4.2.2. Methyl 4,5-dimethoxy-2-phenylaminobenzoate (3b). According to the typical procedure, ester **3b** was obtained from commercially available methyl 2-amino-4,5-dimethoxybenzoate (**2b**) in 85% yield as a white solid after purification by column chromatography (CH_2Cl_2) followed by crystallization from hexanes: mp 139–140 °C (hexanes); ^1H NMR ($CDCl_3$) δ 3.77 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.81 (s, 1H, H_{arom}), 7.02–7.07 (m, 1H, H_{arom}), 7.21–7.35 (m, 4H, H_{arom}), 7.40 (s, 1H, H_{arom}), 9.41 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 51.3, 55.6, 56.1 (OCH_3), 97.4 (CH), 103.4 (C), 112.7, 121.3, 122.8, 129.2 (CH), 140.8, 141.2, 143.9, 154.3 (C), 168.2 (CO); IR (KBr) 3273 (NH), 1661 (CO); MS (EI) *m*/*z* (%) 287 (M^+, 42), 272 (50), 255 (37), 240 (45), 212 (100), 184 (25); HRMS calcd for $C_{16}H_{17}NO_4$: 287.1158, found: 287.1158.

4.2.3. Methyl 4-chloro-2-phenylaminobenzoate (3c). According to the typical procedure, ester **3c** was obtained from commercially available methyl 2-amino-4-chlorobenzoate (**2c**) in 71% yield as a yellow oil after purification by column chromatography (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.66–6.67 (m, 1H, H_{arom}), 6.69–7.41 (m, 6H, H_{arom}), 7.89 (d, *J*=8.6, 1H, H_{arom}), 9.56 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 51.8 (OCH_3), 109.9 (C), 113.2, 117.1, 123.2, 124.4, 129.5, 132.9 (CH), 139.7, 140.5, 149.0 (C), 168.3 (CO); IR (film) 3308 (NH), 1684 (CO); MS (EI) *m*/*z* (%) 263 (M^++2, 77), 261 (M^+, 93), 231 (91), 229 (100), 201 (71); HRMS calcd for $C_{14}H_{12}ClNO_2$: 261.0557, found: 261.0554.

4.2.4. Methyl 5-fluoro-2-phenylaminobenzoate (3d). According to the typical procedure, ester **3d** was obtained from commercially available methyl 2-amino-5-fluorobenzoate (**2d**) in 85% yield as a yellow oil after purification by column chromatography (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.04 (s, 3H, OCH_3), 7.17–7.26 (m, 2H, H_{arom}), 7.35–7.39 (m, 3H, H_{arom}), 7.46–7.51 (m, 2H, H_{arom}), 7.77–7.81 (m, 1H, H_{arom}), 9.46 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 51.8 (OCH_3), 112.1 (d, *J*=6.8, C), 115.5 (d, *J*=7.1, CH), 116.6 (d, *J*=23.5, CH), 121.6 (d, *J*=23.0, CH), 121.8, 123.3, 129.3 (CH), 140.8 (C), 144.3 (d, *J*=1.3, C), 155.6 (d, *J*=236.1, C), 167.7 (d, *J*=3.0, CO); IR (film) 3319 (NH), 1690 (CO); MS (EI) *m*/*z* (%) 245 (M^+, 9), 213 (24), 185

(100); HRMS calcd for $C_{14}H_{12}FNO_2$: 245.0852, found: 245.0853.

4.2.5. Methyl 3-phenylaminothiophene-2-carboxylate (3e). According to the typical procedure, ester **3e** was obtained from commercially available methyl 3-aminothiophene-2-carboxylate (**2e**) in 69% yield as a yellowish solid after purification by column chromatography (CH_2Cl_2) followed by crystallization from Et_2O: mp 66–67 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H, OCH_3), 7.04–7.20 (m, 4H, H_{arom}), 7.31–7.37 (m, 3H, H_{arom}), 8.81 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 51.3 (OCH_3), 102.8 (C), 117.8, 120.2, 122.9, 129.3, 131.7 (CH), 141.3, 151.3 (C), 165.0 (CO); IR (KBr) 3331 (NH), 1667 (CO); MS (EI) *m/z* (%) 233 (M^+, 44), 201 (100), 173 (32); HRMS calcd for $C_{12}H_{11}NO_2S$: 233.0511, found: 233.0519.

4.2.6. Methyl 4-cyano-3-phenylaminothiophene-2-carboxylate (3f). According to the typical procedure, aminoester **3f** was obtained from commercially available methyl 3-amino-4-cyanothiophene-2-carboxylate (**2f**) in 57% yield as a white solid after purification by column chromatography (CH_2Cl_2) followed by crystallization from Et_2O: mp 159–160 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H, OCH_3), 7.19–7.26 (m, 3H, H_{arom}), 7.36–7.41 (m, 2H, H_{arom}), 7.89 (s, 1H, H_{arom}), 8.62 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 51.9 (OCH_3), 103.2 (C), 105.3 (C), 112.8 (CN), 123.9, 125.9, 129.1, 141.3 (CH), 139.4, 151.1 (C), 163.9 (CO); IR (KBr) 3331 (NH), 2228 (CN), 1667 (CO); MS (EI) *m/z* (%) 258 (M^+, 75), 226 (100), 197 (53), 154 (22), 120 (40), 77 (62); HRMS calcd for $C_{13}H_{10}N_2O_2S$: 258.0463, found: 258.0467.

4.3. Typical procedure for the amidation reaction. Preparation of *para*-methoxyphenylamides 4a–f and 7

4.3.1. Synthesis of *N*-(4-methoxyphenyl)-2-phenylaminobenzamide (4a). A solution of $AlMe_3$ (8.81 mmol, 2.0 M in toluene) was added dropwise to a cooled (0 °C) suspension of *para*-anisidine (1.08 g, 8.81 mmol) in CH_2Cl_2 (45 mL). When the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for 45 min until the gas evolution ceased. Then, a solution of methyl *N*-phenylanthranilate (**3a**) (1.00 g, 4.40 mmol) in CH_2Cl_2 (8 mL) was added and the mixture was heated under reflux overnight. The reaction mixture was cooled to room temperature and was carefully quenched with 5% aq HCl (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (15 mL). Then, the organic layer was dried over sodium sulfate, filtered, and the solvent was evaporated at reduced pressure. The resulting residue was purified by crystallization from Et_2O to afford benzamide **4a** (69%) as a white solid.[12]

4.3.2. 4,5-Dimethoxy-*N*-(4-methoxyphenyl)-2-phenylaminobenzamide (4b). According to the typical procedure, benzamide **4b** was obtained from *N*-phenylaminoester **3b** in 69% yield as a white solid after purification by crystallization from Et_2O: mp 122–123 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.76–6.93 (m, 4H, H_{arom}), 6.99–7.02 (m, 2H, H_{arom}), 7.19–7.36 (m, 5H, H_{arom}), 8.44 (br s, 1H, NH), 8.96 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.8, 56.5 (OCH_3), 102.5, 111.8 (CH), 113.3 (C), 114.0, 118.7, 121.6, 122.8, 129.4 (CH), 130.8, 139.2, 142.7, 142.9, 152.4, 156.2 (C), 166.4 (CO); IR (KBr) 3313 (NH), 1638 (CO); MS (EI) *m/z* (%) 378 (M^+, 7), 256 (27), 212 (100), 184 (25), 154 (14); HRMS calcd for $C_{22}H_{22}N_2O_4$: 378.1580, found: 378.1579.

4.3.3. 4-Chloro-*N*-(4-methoxyphenyl)-2-phenylaminobenzamide (4c). According to the typical procedure, benzamide **4c** was obtained from *N*-phenylaminoester **3c** in 70% yield as a white solid after purification by crystallization from Et_2O: mp 144–145 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, OCH_3), 6.70–6.74 (m, 1H, H_{arom}), 6.89 (d, J=8.7, 2H, H_{arom}), 7.05–7.28 (m, 3H, H_{arom}), 7.31–7.46 (m, 6H, H_{arom}), 7.77 (br s, 1H, NH), 9.35 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.4 (OCH_3), 114.2, 114.5 (CH), 116.0 (C), 117.6, 121.7, 122.8, 123.5, 128.6, 129.4 (CH), 130.1, 138.7, 140.2, 147.2, 156.9 (C), 167.1 (CO); IR (KBr) 3308 (NH), 1637 (CO); MS (EI) *m/z* (%) 354 (M^++2, 4), 352 (M^+, 11), 230 (24), 195 (100), 167 (70); HRMS calcd for $C_{20}H_{17}ClN_2O_2$: 352.0979, found: 352.0982.

4.3.4. 5-Fluoro-*N*-(4-methoxyphenyl)-2-phenylaminobenzamide (4d). According to the typical procedure, benzamide **4d** was obtained from *N*-phenylaminoester **3d** in 70% yield as a white solid after purification by crystallization from Et_2O: mp 144–145 °C (Et_2O); ^1H NMR ($CDCl_3$) 3.81 (s, 3H, OCH_3), 6.90 (d, J=8.9, 2H, H_{arom}), 6.97–7.11 (m, 4H, H_{arom}), 7.28–7.36 (m, 4H, H_{arom}), 7.43 (d, J=8.8, 2H, H_{arom}), 7.98 (br s, 1H, NH), 8.54 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.4 (OCH_3), 114.0 (d, J=23.4, CH), 119.0 (d, J=30.0, CH), 114.1, 118.9, 119.5 (CH), 121.1 (d, J=5.7, C), 122.1, 122.8, 129.3 (CH), 130.2, 140.9, 142.0, 156.8 (C), 155.7 (d, J=239.0, C), 166.2 (CO); IR (KBr) 3308 (NH), 1643 (CO); MS (EI) *m/z* (%) 336 (M^+, 65), 214 (86), 185 (99), 123 (100), 108 (80), 77 (26); HRMS calcd for $C_{20}H_{17}FN_2O_2$: 336.1274, found: 336.1273.

4.3.5. *N*-(4-Methoxyphenyl)-3-phenylaminothiophene-2-carboxamide (4e). According to the typical procedure, amide **4e** was obtained from *N*-phenylaminoester **3e** in 82% yield as a white solid after purification by crystallization from Et_2O: mp 136–138 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, OCH_3), 6.88–6.90 (m, 2H, H_{arom}), 7.00–7.04 (m, 1H, H_{arom}), 7.13–7.43 (m, 9H, H_{arom}+NH), 9.40 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.4 (OCH_3), 114.1, 119.6, 119.7, 122.4, 122.9, 127.5, 129.2 (CH), 105.6, 130.4, 141.8, 150.1, 156.6 (C), 163.2 (CO); IR (KBr) 3296 (NH), 1590 (CO); MS (EI) *m/z* (%) 324 (M^+, 46), 201 (95), 173 (81), 158 (65), 123 (100), 108 (72), 77 (53); HRMS calcd for $C_{18}H_{16}N_2O_2S$: 324.0932, found: 324.0936.

4.3.6. 4-Cyano-*N*-(4-methoxyphenyl)-3-phenylaminothiophene-2-carboxamide (4f). According to the typical procedure, amide **4f** was obtained from *N*-phenylaminoester **3f** in 68% yield as a white solid after purification by crystallization from Et_2O: mp 133–134 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), 6.80 (d, J=8.8, 2H, H_{arom}), 6.98 (d, J=7.9, 2H, H_{arom}), 7.08 (t, J=7.3, 1H, H_{arom}), 7.27–7.31 (m, 4H, H_{arom}), 7.87 (s, 1H, H_{arom}), 7.88 (br s, 1H, NH), 8.41 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.3 (OCH_3), 107.7 (C), 112.9 (CN), 114.0, 119.5, 122.6,

123.7, 129.3 (CH), 129.7 (C), 137.7 (CH), 141.6, 145.3, 156.8 (C), 163.2 (CO); IR (KBr) 3284 (NH), 2250 (CN), 1596 (CO); MS (EI) *m/z* (%) 349 (M^+, 46), 227 (89), 198 (59), 172 (11), 131 (16), 123 (100), 108 (69); HRMS calcd for $C_{19}H_{15}N_3O_2S$: 349.0885, found: 349.0883.

4.3.7. *N*-(4-Methoxyphenyl)-3-phenylaminopropionamide (7). According to the typical procedure, amide **7** was obtained from ethyl 3-phenylaminopropionate[18] (**6**) in 72% yield as a white solid after purification by crystallization from Et_2O: mp 100–101 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 2.62 (t, J=5.8, 2H, CH_2), 3.54 (t, J=5.8, 2H, CH_2), 3.77 (s, 3H, OCH_3), 6.66–6.85 (m, 5H, H_{arom}), 7.17–7.37 (m, 5H, H_{arom}+NH), 7.54 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 36.2, 40.1 (CH_2), 55.4 (OCH_3), 113.3, 113.9, 118.0, 121.9, 129.3 (CH), 130.6, 147.5, 156.3 (C), 170.0 (CO); IR (KBr) 3296 (NH), 1655 (CO); MS (EI) *m/z* (%) 270 (M^+, 20), 165 (29), 123 (41), 108 (43), 106 (100), 77 (67), 51 (31); HRMS calcd for $C_{16}H_{18}N_2O_2$: 270.1368, found: 270.1364.

4.4. Typical procedure for the PIFA-mediated cyclization. Preparation of indazol-3-ones 1a,c,d and pyrazolones 1f and 8

4.4.1. 2-(4-Methoxyphenyl)-1-phenyl-1,2-dihydro-3*H*-indazol-3-one (1a). A solution of PIFA (202 mg, 0.46 mmol) in 46 mL of CH_2Cl_2 was added at 0 °C to a solution of benzamide **4a** (100 mg, 0.32 mmol) and TFA (0.08 mL, 0.94 mmol) in 32 mL of the same solvent, and the new solution was stirred for 1 h. Then, the solvent was evaporated at reduced pressure and the resulting residue was purified by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes to afford indazolone **1a** as a white solid (61%).[12]

4.4.2. 6-Chloro-2-(4-methoxyphenyl)-1-phenyl-1,2-dihydro-3*H*-indazol-3-one (1c). According to the general procedure, indazolone **1c** was obtained from benzamide **4c** in 81% yield as a white solid after purification by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes: mp 142–143 °C (hexanes); ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H, OCH_3), 6.84 (d, J=8.9, 2H, H_{arom}), 7.14–7.39 (m, 7H, H_{arom}), 7.42 (d, J=8.9, 2H, H_{arom}), 7.85–7.87 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 55.2 (OCH_3), 112.2, 114.1 (CH), 116.4 (C), 123.9, 124.5, 125.3, 125.4, 127.8 (CH), 128.1 (C), 129.6 (CH), 139.0, 141.0, 149.9, 157.9 (C), 161.6 (CO); IR (KBr) 1690 (CO); MS (EI) *m/z* (%) 352 (M^++2, 18), 350 (M^+, 70), 335 (100), 307 (78), 279 (37); HRMS calcd for $C_{20}H_{15}ClN_2O_2$: 350.0822, found: 350.0817.

4.4.3. 5-Fluoro-2-(4-methoxyphenyl)-1-phenyl-1,2-dihydro-3*H*-indazol-3-one (1d). According to the general procedure, indazolone **1d** was obtained from benzamide **4d** in 77% yield as a pale brown oil after purification by column chromatography (hexanes/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 3.73 (s, 3H, OCH_3), 6.84 (d, J=8.8, 2H, H_{arom}), 7.08–7.11 (m, 1H, H_{arom}), 7.22–7.25 (m, 4H, H_{arom}), 7.32–7.37 (m, 2H, H_{arom}), 7.58–7.61 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 55.1 (OCH_3), 109.2 (d, J=24.1, CH), 113.8 (d, J=8.0, CH), 114.0 (CH), 118.7 (d, J=9.0, C), 121.1 (d, J=26.0, CH), 124.4, 125.3, 127.7 (CH), 127.9 (C), 129.5 (CH), 141.5, 146.1, 157.9 (C), 158.9 (d, J=243.1, C), 161.5 (CO); IR (film) 1684 (CO); MS (EI) *m/z* (%) 334 (M^+, 73), 319 (75), 263 (93), 184 (100), 157 (62); HRMS calcd for $C_{20}H_{15}FN_2O_2$: 334.1118, found: 334.1113.

4.4.4. 6-Cyano-2-(4-methoxyphenyl)-1-phenylthieno[3,2-*c*]pyrazol-3-one (1f). According to the general procedure, pyrazolone **1f** was obtained from amide **4f** in 61% yield as a brownish oil after purification by column chromatography (hexanes/EtOAc, 1:1); ^1H NMR ($CDCl_3$) δ 3.74 (s, 3H, OCH_3), 6.85 (d, J=8.6, 2H, H_{arom}), 7.33–7.35 (m, 7H, H_{arom}), 8.20 (s, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 55.3 (OCH_3), 97.8, 111.6 (C), 114.3 (CH), 115.3 (CN), 125.8, 126.6 (CH), 127.7 (C), 129.4, 129.6, 146.3 (CH), 138.7, 154.9, 158.1 (C), 158.7 (CO); IR (film) 2290 (CN), 1678 (CO); MS (EI) *m/z* (%) 347 (M^+, 72), 332 (97), 219 (22), 131 (49), 123 (11), 69 (100); HRMS calcd for $C_{19}H_{13}N_3O_2S$: 347.0728, found: 347.0728.

4.4.5. 2-(4-Methoxyphenyl)-1-phenylpyrazol-3-one (8). According to the general procedure, but using TFEA as solvent instead of the combination of CH_2Cl_2/TFA, pyrazolone **8** was obtained from amide **7** in 35% yield as a white solid after purification by column chromatography (hexanes/EtOAc, 1:1) followed by crystallization from hexanes: mp 99–100 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 2.70 (t, J=7.1, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.99 (t, J=7.1, 2H, CH_2), 6.83 (d, J=8.7, 2H, H_{arom}), 6.96–7.06 (m, 3H, H_{arom}), 7.24–7.30 (m, 2H, H_{arom}), 7.72 (d, J=8.7, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 31.3, 54.9 (CH_2), 55.3 (OCH_3), 113.9, 118.4, 120.0, 123.5, 129.1 (CH), 131.4, 149.7, 156.2 (C), 171.1 (CO); IR (KBr) 1696 (CO); MS (EI) *m/z* (%) 268 (M^+, 80), 212 (57), 135 (90), 118 (96), 77 (100), 51 (38); HRMS calcd for $C_{16}H_{16}N_2O_2$: 268.1212, found: 268.1218.

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Supplementary data

Supplementary data associated with this article, which include ^1H NMR and ^{13}C NMR spectra of all new compounds, can be found in the online version, at doi:10.1016/j.tet.2006.09.031.

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