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A microwave assisted synthesis of benzoxazoles from carboxylic acids

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ABSTRACT

A series of various poly-substituted benzoxazoles were synthesized starting from readily available carboxylic acids. The method is based on TCT (cyanuric chloride)/microwave acid activation and it is characterized by mild conditions, allowing for a wide range of starting materials and functionalization of final products.

1. Introduction

The benzoxazole ring is a core structure found in a wide class of natural and synthetic compounds showing biological properties, such as natural antimycobacterials,[1] non-nucleoside reserve transcriptase inhibitors,[2] peroxisome proliferators activated receptor γ antagonists,[3] cathepsin S inhibitors,[4] cytotoxic natural products,[5] 5-HT3 receptor antagonists,[6] estrogen receptor-β agonists,[7] anticancer agents,[8] and elastase inhibitors.[9] Benzoxazoles also find applications in agricultural field, as herbicides,[10] and in technological fields, as whitening agents and laser dyes,[11] in organic light emitting diodes (OLEDs),[12] and polymer production.[13]

Benzoxazoles are usually synthesized from 2-aminophenols, by coupling with carboxylic acid derivatives or by oxidative cyclization of a phenolic imine intermediate.[14] The first route requires strongly acidic conditions (usually polyphosphoric acid), high temperatures, and long reaction times,[15] whereas the second route requires strong oxidants.[14,16] A milder oxidative cyclization is also reported, employing *N*-iodosuccinimide.[17] *ortho*-Haloanilides are another class of starting material often employed to give 2-substituted benzoxazoles through metal-catalyzed cyclization.[10,18] Apart from cyclization reactions, 2-substituted benzoxazoles are prepared by arylation, alkylation, and amination of the benzoxazole moiety, via metal-catalyzed C–H bond activation.[19] Recent examples of benzoxazole synthesis include the employment of the Shvo catalyst under hydrogen transfer catalysis[20] and the use of the Hantzsch ester for reductive cyclization.[21]

Despite the numbers of reported methods, benzoxazole synthesis often suffers limitations, due to harsh reaction conditions, the particular reagents involved or the preparation of starting materials thus limiting functionalization of final products (often restricted to 2-arylbenzoxazoles). Moreover, reagents, such as PPA,[15] $SOCl_2$, *p*-TsOH, oxidants or metal-based reagents catalysts[18] are frequently used in large amounts or excess, making product purification difficult. The result is a series of methods mainly addressed to 2-arylbenzoxazole syntheses, with decreasing yields with different substrates. In this context, improvements, both in terms of mildness and efficiency, would be of worth.

2. Results and discussion

We have already investigated the use of TCT (cyanuric chloride, 2,4,6-trichloro-1,3,5-triazine, **2a**) derivatives to activate carboxylic acids, as an alternative method to the use of acid chlorides.[22] The use of carboxylic acids as starting materials provides a wider range of different building blocks for heterocycle functionalization, compared to acid chlorides,[23] and the mildness of this kind of activation avoids the use of harsh chlorinating reagents (like $SOCl_2$), allowing an easy extension to amino acids and leading to the synthesis of chiral 2-substituted benzoxazoles.

In order to define the conditions of the reaction, we tested the process using benzoic acid as a representative substrate (Scheme 1). A two-steps synthetic protocol was developed consisting of activation of a carboxylic acid with a triazine derivative **2** followed by

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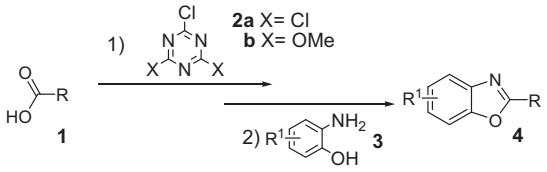


Scheme 1. Two steps synthesis of 2-substituted benzoxazoles.

reaction of the activated acid with 2-aminophenol through formation of amide and subsequent cyclization.

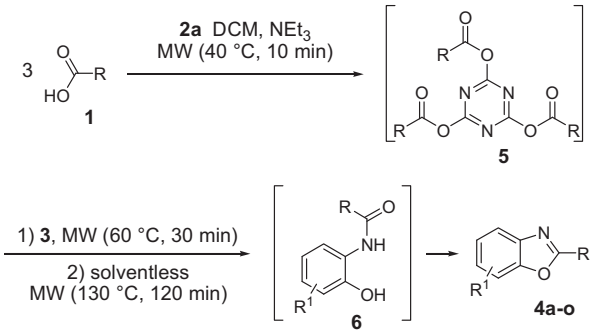
In the first stage we evaluated the use of both TCT (**2a**)[24] and the corresponding alkoxide derivative CDMT (2-chloro-4,6-dimethoxy-1,3,5-triazine, **2b**),[25] aiming to an activation process as efficient as possible, while keeping at the same time the mildness of the method. Activation of the acid with TCT was carried out in presence of triethylamine (1 equiv respect to acid) in dry DCM, checking the effect of different TCT/acid ratios (1:1–1:3) and the influence of temperature. Thus, using TCT, we carried out reactions at room temperature and under a slight heating (both through thermal and microwave irradiation). Activation with CDMT was instead conducted in dry THF in the presence of NMM (*N*-methylmorpholine), with an acid/CDMT/NMM ratio of 1:1:1 at room temperature for 1 h. The yields of the first stage could not directly evaluated as the intermediate cannot be isolated and the efficiency of the first step was therefore calculated taking into account the final yields of a standard reaction. Use of TCT generally gave good results while all tests employing CDMT led to poor yields (less than 10%).

The effects of solvents and heating parameters were investigated to optimize reaction conditions of second stage. Other than leading the second stage in the starting DCM solution, we evaluate the addition of DMF, NMP, THF, and toluene as a co-solvent.

Reports on solvent-free reactions have become increasingly frequent and the field has developed into an important branch of synthetic chemistry.[26] Recently, much attention has focused on microwave assisted organic reactions in the absence of solvent.[27] The reaction was therefore checked under solvent-free conditions, by removing the starting solvent by flushing the reaction mixture with nitrogen after the addition of 2-aminophenol. Warming of the reaction mixture was conducted by both thermal heating and microwave irradiation. Temperature was tested ranging from 70 to 170 °C (higher temperatures were reached by microwave irradiation in closed vessel) and reaction times varied from 30 min to 2 h.

So, the carboxylic acid (1 equiv) was activated with 1/3 equiv TCT (**2a**) and NEt_3 in dry DCM under a slight microwave irradiation (40 °C, 20 W max, 10 min). The intermediate esters **5**, formed by substitution of all chlorine atoms by carboxylate ions on the triazine ring, were not isolated but directly reacted with 2-aminophenol. After heating reaction mixture to 60 °C (50 W max power) for 30 min, DCM was evaporated by means of a gentle stream of nitrogen and the subsequent solvent-free reaction mixture heated to 130 °C for 120 min (50 W max power). Formation of intermediate amide **6**, followed by cyclization, gives 2-substituted benzoxazoles (Scheme 2). The crude reaction mixture was extracted with a DCM/EtOAc mixture, causing the precipitation of triazine byproducts and ammonium salts and allowing an easy chromatographic purification of desired products.

This methodology was successfully employed to prepare different aliphatic and aromatic 2-substituted benzoxazoles **4** in moderate to good conversions (Table 1, entries 1–12). In order to evaluate the reactivities of the different starting materials, the cyclization process was always conducted heating to 130 °C for 2 h (50 W max power). All reactions furnished the benzoxazoles, the other product being the unreacted amides. The synthetic protocol



Scheme 2. Synthetic path to 2-substituted benzoxazoles.

Table 1
Conversion to benzoxazoles (standard 2 h reaction time)[29]

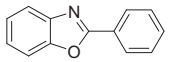
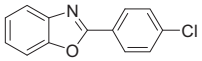
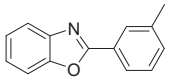
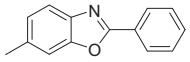
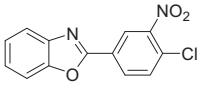
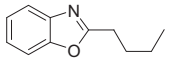
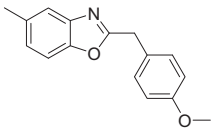
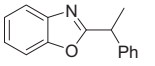
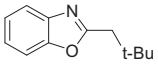
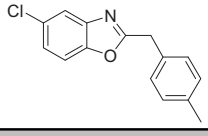
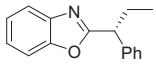
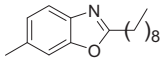
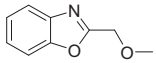
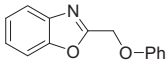
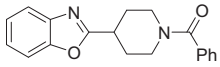
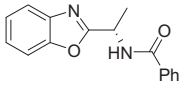
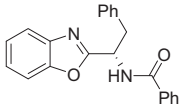
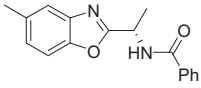
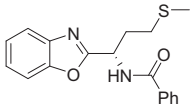
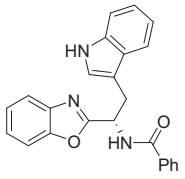
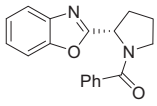
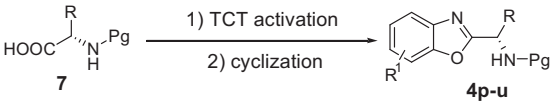
Entry	Compound		Conversion
1	**4a**		82%
2	**4b**		68%
3	**4c**		78%
4	**4d**		79%
5	**4e**		71%
6	**4f**		74%
7	**4g**		70%
8	**4h**		74%
9	**4i**		72%
10	**4j**		49%

Table 1 (*continued*)

Entry	Compound		Conversion
11	**4k**		73%
12	**4l**		70%
13	**4m**		72%
14	**4n**		71%
15	**4o**		69%
16	**4p**		57%
17	**4q**		71%
18	**4r**		49%
19	**4s**		58%
20	**4t**		61%
21	**4u**		55%

was then applied to α-hydroxy and natural α-amino acid derivatives, to include low cost chiral substituents into the 2-position of the heterocycle (Scheme 3). Examination of the data collected showed that only little variation of the conversions could be noted even when the starting amide contained the substituted phenyl group. Only in the case of the benzoxazole **4j** derived from 2-amino-5-chlorophenol (Table 1, entry 10) was the conversion <50% after 2 h. Good results were obtained employing methoxyacetic and phenoxyacetic acids, also (Table 1, entries 13, 14).

Synthesis of benzoxazoles starting from natural α-amino acids required protection of the amino group. The preliminary reactions, carried out with *N*-Boc protected amino acids were unsuccessful, as only the intermediate amides **6** were recovered and in low yields (<15%) at the end of the overall process. Even the use of other



Scheme 3. Synthesis of *N*-{1-(benzo[*d*]oxazol-2-yl)alkyl}benzamides.

carbamate protecting groups, like *N*-Cbz and *N*-Fmoc, did not lead to the desired products. An accurate investigation showed that the reactions occurred until the formation of the amide, and the drawback was found to be in the cyclization step. In fact we observed degradation of carbamate protecting groups during cyclization step, thus allowing side reactions.[28] Finally, the choice of the *N*-benzoyl protecting group was found to be correct for the synthesis of 1-(benzo[*d*]oxazol-2-yl)alkylamines **4p**–**u**. Benzoxazole synthesis starting from *N*-benzoyl α-amino acids gave satisfactory results, leading to the final products in good yields (>60%) after purification. In this case the cyclization step required longer reaction times: standard 120 min reaction time always gave a mixture of only final product and intermediate amide, and when prolonging the reaction time, the formation of side products appeared to be consistent. However, in this way we could prepare protected 1-(benzo[*d*]oxazol-2-yl)alkylamines as pure products. Previous reports on the synthesis of 2-benzoxazoles indicated good yields only with *Z*-proline,[18a] while in other cases, approximate yields from 11 to 33% of not analytically pure products could only be achieved.

3. Conclusion

In conclusion, here we propose a useful method for the synthesis of benzoxazoles, starting directly from readily available acids. A mild activation process allows the use of a wide range of starting materials, so allowing the functionalization of final products, and avoids extra steps to prepare starting materials. Furthermore, cheap, easy-to-handle reagents, and simple workup make this method very practical. Energetic consumption and solvent required are low, making this method an interesting improvement also in terms of green chemistry. Moreover it was possible to produce an interesting class of benzoxazole starting from natural amino acids.

4. Experimental

4.1. General methods

All reagents and solvents employed were purchased from Sigma–Aldrich. Reagents were used without further purification. Solvents were dried and distilled by usual methods. Microwave reactions were carried out using a CEM Discover instrument (CEM Corporation), in a 10 mL glass tube (CEM designed 10 mL pressure-rated reaction vial), under a nitrogen atmosphere. Temperature was monitored by an infrared monitoring system. TLC analysis was performed with Merck Kieselgel 60 F_{254} plates and spots visualized using UV light at 254 nm. Flash-column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Melting points were determined in open capillary tubes on a Buchi apparatus and are uncorrected. Optical rotations were measured on Jasco P1010 polarimeter. IR were recorded on Jasco FT-IR480plus spectrometer. Elemental analyses were performed on Perkin–Elmer Elemental Analyzer 240B. ^{1}H NMR and ^{13}C NMR were recorded at 300 and 75.4 MHz, in $CDCl_3$, with TMS as an internal standard and chemical shifts are given in parts per million (multiplicity: s=singlet, d=doublet, dd=double doublet, t=triplet, q=quadruplet, quint=quintuplet, m=multiplet). The *N*-benzoyl derivatives of the α-amino acids were prepared according to literature procedures,[30]

and identified by comparison with published data (^{1}H and ^{13}C NMR, melting point, optical rotation).

4.2. Typical procedure for the preparation of 4

In a reaction tube containing a well-stirred solution of the carboxylic acid (1.83 mmol) and NEt_3 (0.25 mL 1.83 mmol) in dry CH_2Cl_2 (3 mL), cyanuric chloride (0.11 g, 0.61 mmol) was added in small amounts at room temperature. The sealed tube was heated by microwave irradiation to 40 °C (max power 20 W) for 10 min. 2-Aminophenol (0.18 g, 1.66 mmol) was then added, and the closed vessel was irradiated at 60 °C (max power 50 W) for 30 min. Solvent was then removed by a gentle stream of nitrogen, giving a semi-solid residue. The sealed tube was then irradiated at 130 °C (max power 50 W) for 120 min. The reaction mixture was then extracted with EtOAc/DCM (1:1) and the crude products were purified by silica gel column chromatography (EtOAc/hexane 1:9 for **4a**–**n** and 4:6 for **4o**–**u**) to afford desired benzoxazoles.

*4.2.1. 2-(4-Chloro-3-nitrophenyl)benzo[d]oxazole (**4e**).* Colourless solid: mp 192 °C; IR (film) ν (cm^{-1}) 2920, 2850, 1527, 1449, 1343, 1239, 1071, 807, 749; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.44 (m, 2H), 8.74 (d, *J* 2.0 Hz, 1H), 8.38 (dd, *J* 2.0 Hz, 8.4 Hz, 1H), 7.79–7.82 (m, 1H), 7.72 (d, *J* 8.4 Hz, 1H), 7.60–7.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 150.9, 148.4, 141.7, 132.7, 131.3, 129.8, 127.2, 126.2, 125.2, 124.4, 120.6, 110.9; Anal. Calcd for $C_{13}H_7ClN_2O_3$: C, 56.85; H, 2.57; N, 10.20. Found: C, 56.90; H, 2.49; N, 10.24.

*4.2.2. 2-(4-Methoxybenzyl)-5-methylbenzo[d]oxazole (**4g**).* Orange oil; IR (film) ν (cm^{-1}) 2930, 2835, 1776, 1612, 1570, 1513, 1249, 1178, 1034, 801; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.30–7.25 (m, 3H), 7.05 (d, *J* 8.2 Hz, 1H), 6.86–6.81 (m, 2H), 4.16 (s, 2H), 3.73 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 158.6, 149.1, 141.2, 133.8, 129.8, 126.7, 125.5, 119.4, 114.0, 109.6, 55.0, 34.2, 21.2; Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.92; H, 6.05; N, 5.51.

*4.2.3. 5-Chloro-2-[(4-methylphenyl)methyl]benzo[d]oxazole (**4j**).* Yellow solid: mp 52–54 °C; IR (film) ν (cm^{-1}) 2923, 1565, 1515, 1452, 1427, 1256, 1143, 1054, 805; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* 2.1 Hz, 1H), 7.35–7.13 (m, 6H), 4.20 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 149.5, 142.4, 137.0, 131.2, 129.5, 129.5, 128.8, 124.8, 119.7, 111.0, 34.8, 21.0; Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69; N, 5.43. Found: C, 69.80; H, 4.72; N, 5.50.

*4.2.4. 2-[(R)-1-Phenylpropyl]benzo[d]oxazole (**4k**).* Orange oil; $[\alpha]_D^{20}$ +2.86 (*c* 0.14, MeOH); IR (film) ν (cm^{-1}) 3029, 2963, 2927, 2873, 1566, 1455, 1242, 746, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.73 (m, 1H), 7.20–7.44 (m, 8H), 4.12 (t, *J* 7.8 Hz, 1H), 2.34–2.49 (m, 1H), 2.07–2.21 (m, 1H), 0.97 (t, *J* 3.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 150.7, 141.2, 139.7, 128.6, 127.9, 127.2, 124.5, 124.0, 119.7, 110.4, 47.8, 27.5, 12.2; Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.92; H, 6.40; N, 5.95.

*4.2.5. 6-Methyl-2-nonylbenzo[d]oxazole (**4l**).* Pale yellow oil; IR (film) ν (cm^{-1}) 2925, 2854, 1613, 1574, 1487, 1465, 1246, 1117, 941, 810; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* 8.1 Hz, 1H), 7.26 (s, 1H), 7.09 (d, *J* 8.1 Hz, 1H), 2.89 (t, *J* 7.7 Hz, 2H), 2.45 (s, 3H), 1.86 (quint, *J* 7.5 Hz, 2H), 1.42–1.26 (m, 12H), 0.87 (t, *J* 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 151.0, 139.1, 134.5, 125.0, 118.7, 110.3, 31.8, 29.3, 29.2, 29.2, 29.1, 28.5, 26.7, 22.6, 21.5, 14.0; Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.80; H, 9.76; N, 5.44.

*4.2.6. 2-(Methoxymethyl)benzo[d]oxazole (**4m**).* Dark yellow oil; IR (film) ν (cm^{-1}) 2917, 2850, 1781, 1731, 1455, 1101, 744, 612; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.75 (m, 1H), 7.52–7.55 (m, 1H), 7.33–7.36 (m, 2H), 4.71 (s, 2H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 150.7, 140.7, 125.2, 124.3, 120.1, 110.6, 66.8, 59.1; Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.17; H, 5.59; N, 8.62.

*4.2.7. {4-(Benzo[d]oxazol-2-yl)piperidin-1-yl}(phenyl)methanone (**4o**).* Dark green oil; IR (film) ν (cm^{-1}) 3058, 2952, 2925, 2858, 1632, 1568, 1455, 1435, 1279, 1244, 1145, 1005, 747, 709; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.72 (m, 1H), 7.47–7.53 (m, 1H), 7.41 (s, 5H), 7.29–7.35 (m, 2H), 4.66 (b, 1H), 3.87 (b, 1H), 3.21 (m, 3H), 2.00–2.27 (b, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 167.8, 150.5, 140.9, 135.8, 129.5, 128.4, 126.7, 124.7, 124.2, 119.6, 110.3, 46.7, 35.8, 29.4; Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.52; H, 5.97; N, 9.21.

*4.2.8. N-{(S)-1-(Benzo[d]oxazol-2-yl)ethyl}benzamide (**4p**).* Colourless solid: mp 191 °C; $[\alpha]_D^{20}$ +4.21 (*c* 0.66, DCM); IR (film) ν (cm^{-1}) 3283, 2933, 1636, 1611, 1572, 1528, 1457, 1243, 757, 700; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* 6.9 Hz, 2H), 7.66–7.69 (m, 1H), 7.47–7.52 (m, 2H), 7.39–7.44 (m, 2H), 7.30–7.33 (m, 2H), 7.22 (b, 1H), 5.61 (q, *J* 7.0 Hz, 1H), 1.73 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 166.6, 150.9, 140.6, 133.7, 131.8, 128.6, 127.1, 125.2, 124.5, 119.9, 110.8, 44.4, 20.1; Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.07; H, 5.35; N, 10.40.

*4.2.9. N-{(S)-1-(Benzo[d]oxazol-2-yl)-2-phenylethyl}benzamide (**4q**).* Pale red solid: mp 181 °C; $[\alpha]_D^{20}$ −5.32 (*c* 0.53, DCM); IR (film) ν (cm^{-1}) 3304, 3060, 3029, 2924, 2853, 1644, 1531, 1488, 1455, 1241, 747, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.79 (m, 2H), 7.63–7.66 (m, 1H), 7.47–7.54 (m, 2H), 7.38–7.43 (m, 2H), 7.32–7.35 (m, 2H), 7.18–7.21 (m, 3H), 7.03–7.06 (m, 3H), 5.83–5.90 (m, 1H), 3.41–3.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 165.0, 150.8, 140.5, 135.5, 133.7, 131.8, 129.4, 128.6, 128.5, 127.1, 125.2, 124.5, 119.9, 110.8, 49.4, 39.4; Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.25; H, 5.32; N, 8.13.

*4.2.10. N-{(S)-1-(5-Methylbenzo[d]oxazol-2-yl)ethyl}benzamide (**4r**).* Colourless solid: mp 194–196 °C; $[\alpha]_D^{20}$ −1.85 (*c* 0.26, MeOH); IR (film) ν (cm^{-1}) 3264, 2924, 1761, 1632, 1572, 1532, 1488, 1377, 1258, 1111, 800, 694; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2H), 7.52–7.36 (m, 6H), 7.13 (br d, *J* 8.3 Hz, 1H), 5.65–5.56 (quint, *J* 7.2 Hz, 1H), 2.45 (s, 3H), 1.73 (d, *J* 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 166.6, 149.1, 140.8, 134.3, 133.8, 131.7, 128.5, 127.1, 126.2, 119.7, 110.1, 44.4, 21.4, 20.0; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.76; H, 5.82; N, 10.05.

*4.2.11. N-{(S)-1-(Benzo[d]oxazol-2-yl)-3-(methylthio)propyl}benzamide (**4s**).* Dark yellow oil; $[\alpha]_D^{20}$ −4.06 (*c* 0.32, MeOH); IR (film) ν (cm^{-1}) 3062, 2918, 1758, 1642, 1531, 1483, 1454, 1241, 1104, 744, 710, 613; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.90 (m, 2H), 7.68–7.71 (m, 1H), 7.51–7.56 (m, 2H), 7.33–7.48 (m, 5H), 5.71–5.78 (m, 1H), 2.62–2.68 (m, 2H), 2.30–2.60 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 165.3, 150.8, 140.6, 133.6, 131.9, 128.6, 127.2, 125.3, 124.6, 119.9, 110.8, 47.9, 33.1, 29.9, 29.6, 15.5; Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.21; H, 5.69; N, 8.65.

*4.2.12. N-{(S)-1-(Benzo[d]oxazol-2-yl)-2-(1H-indol-3-yl)ethyl}benzamide (**4t**).* Viscous yellow oil; $[\alpha]_D^{20}$ +14.58 (*c* 0.10, DCM); IR (film) ν (cm^{-1}) 3299 (br), 3057, 2924, 2852, 2359, 1646, 1521, 1487, 1455, 1241, 742, 711; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.70 (d, *J* 7.4 Hz, 2H), 7.60–7.62 (m, 1H), 7.44–7.51 (m, 3H), 7.24–7.37 (m, 5H), 7.11 (t, *J* 7.6 Hz, 1H), 6.95 (t, *J* 7.4 Hz, 2H), 6.80 (b, 1H), 5.90–5.95 (m, 1H), 3.60–3.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 165.6, 150.8, 140.6, 136.0, 133.6, 131.7, 128.4, 127.7, 127.1, 125.0, 124.4, 123.0, 122.1, 119.8, 119.6, 118.4, 111.2, 110.7, 109.5, 49.4, 29.3; Anal. Calcd for

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$C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.71; H, 5.11; N, 11.09.

*4.2.13. {(S)-2-(Benzo[d]oxazol-2-yl)pyrrolidin-1-yl}(phenyl)methanone (**4u**).* Dark green oil; $[\alpha]_D^{20}$ −24.45 (*c* 0.20, DCM); IR (film) ν (cm^{-1}) 3057, 2957, 2924, 2853, 1633, 1574, 1455, 1409, 1242, 748, 702; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69–7.72 (m, 1H), 7.61–7.64 (m, 2H), 7.50–7.53 (m, 1H), 7.41–7.46 (m, 3H), 7.29–7.33 (m, 2H), 5.54–5.58 (m, 1H), 3.83–3.91 (m, 1H), 3.61–3.69 (m, 1H), 2.43–2.55 (m, 1H), 2.16–2.35 (m, 2H), 1.96–2.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 166.4, 150.6, 141.2, 136.1, 130.3, 128.2, 127.4, 124.7, 124.2, 120.0, 110.7, 55.1, 50.1, 31.0, 25.4; Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.89; H, 5.60; N, 9.49.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.084. These data include MOL files and InChiKeys of the most important compounds described in this article.

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