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# Iodine-catalyzed formation of substituted 2-aminobenzothiazole derivatives in $PEG_{400}$†

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An iodine-catalyzed formation of substituted 2-aminobenzothiazole derivatives is herein described using hydrogen peroxide as an oxidant in $PEG_{400}$. The method enabled an efficient environmentally sound access to this valuable scaffold in moderate to excellent yields under metal-free conditions.

## Introduction

Efficient synthesis of 2-aminobenzothiazoles has attracted a lot of attention because of the ubiquity of this heteroaromatic scaffold in pharmaceuticals.[1] This pharmacophore is frequently found in active and natural compounds such as Riluzole®, used as a treatment of amyotrophic lateral sclerosis,[2] R116010, a highly potent and selective inhibitor of all-*trans*-retinoic acid metabolism,[3] and naphthyridone HM13N, described as a promising anti-HIV agent (Fig. 1).[4]

Several methods have been so far described to generate 2-aminobenzothiazoles and apart from approaches starting from various thioureas,[5] most of them are based on isothiocyanates. Isothiocyanates are key precursors involved in protocols requiring transition metal catalysts[6] or using metal-free conditions.[7] However the use of isothiocyanates, often unstable, requires harsh reaction conditions, long reaction times, or the pre-functionalization of the starting material. Recently, isocyanides appeared to be an efficient alternative to synthetize 2-aminobenzothiazole products. Vlaar *et al.*[8] for example recently reported a palladium-catalyzed insertion reaction of isocyanides with functionalized aniline closely followed by the work of Ji *et al.* which described a cobalt[9] or a nickel[10] catalysis to obtain the 2-aminobenzothiazole core in moderate to good yields (Scheme 1a). Despite the efficiency of these methods, the development of a transition metal-free approach is still desirable, since as Bochatay *et al.*[11] pointed out, in the absence of palladium and copper catalysts, 1,3-benzothiazole was formed but without any substituent in C2 when 2-aminothiophenol was exposed to *tert*-butylisocyanide (Scheme 1b).

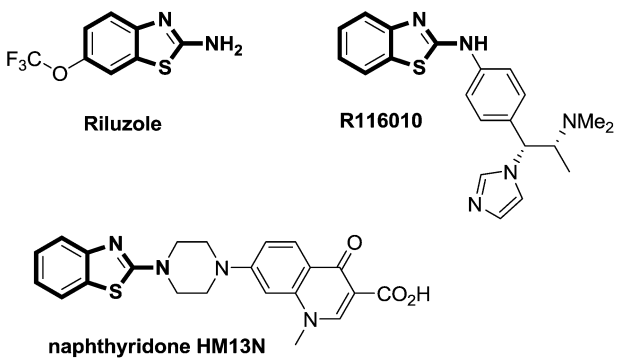
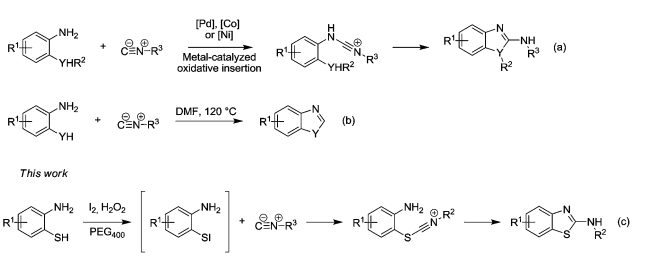



Fig. 1 Selected biologically active molecules that contain the 2-aminobenzothiazole core.

## Results and discussion

Recently iodine-catalyzed oxidative coupling reactions have made rapid advances, making it possible to overcome problems related to the presence of residual metal in transition-metal catalysis.[12] This alternative also offers a greater atom economy process and greener and milder reaction conditions which are therefore tolerated by a broader range of substrates. Based on our previous work on iodine catalyzed sulfenylation in which electrophilic sulfenyl iodide was generated *in situ*,[13] we report herein the possible use of 2-aminothiophenol and isocyanides




Scheme 1 Recent methods for the synthesis of 2-aminobenthiazole derivatives with isocyanides.

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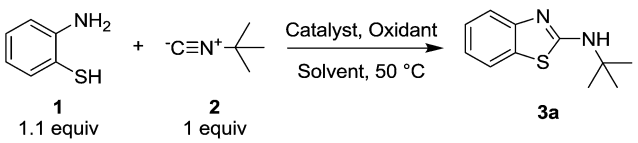
in a transition metal-free procedure to obtain various substituted 2-aminobenzothiazole derivatives (Scheme 1c).

In order to achieve the optimized conditions, 2-aminothiophenol and *tert*-butylisocyanide were selected as model substrates. First iodine in a catalytic amount and hydrogen peroxide as oxidant in $PEG_{400}$ were tested. $PEG_{400}$ is a polymeric eco-friendly non-toxic medium, neutral, non-volatile, odorless and inexpensive, soluble in water and many organic solvents,[14] which was successfully used as solvent in our groups.[13,15] In these conditions, the expected product **3a** was isolated in an excellent 89% yield (Table 1 entry 1). A modification of the oxidant or of the iodinated agent did not lead to a significant improvement (entries 2–7). Then the effect of various solvents was evaluated and the best result was obtained with $PEG_{400}$ compared with either protic or aprotic solvents (entries 8–14). Ethereal solvents such as THF or 1,4-dioxane exhibited slightly lower results with 82 and 79% yields respectively. Hence the optimized conditions were chosen as follows: **1** (1.1 equiv.), **2** (1.0 equiv.), hydrogen peroxide (1.1 equiv.), with iodine (5 mol%) in $PEG_{400}$ at 50 °C for 18 hours.

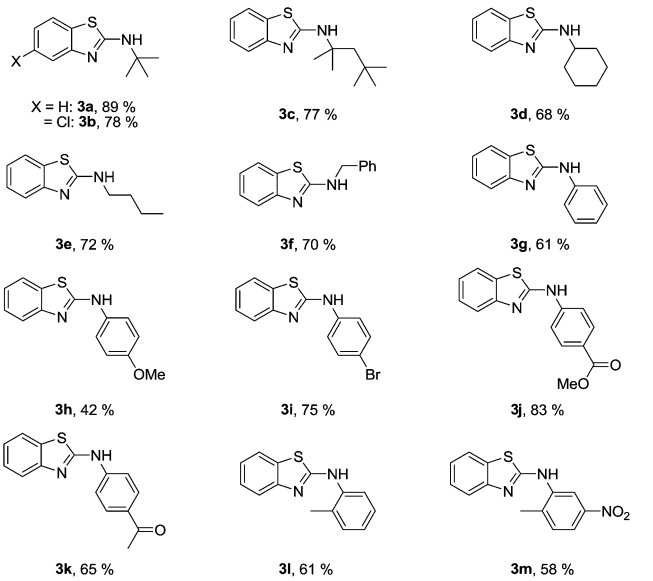
Next, we investigated the reactivity of other isocyanides to evaluate the scope and the generality of this process. Satisfactorily, the transformation proceeded smoothly with a wide range of substrates, leading to the corresponding product **3** in moderate to excellent yields (Scheme 2). The results showed that aliphatic saturated chains featuring a cyclic, linear or branched pattern were well tolerated (products **3a–e**). A benzyl substituent was also successfully introduced (product **3f**). Then various aryl isocyanides bearing electron-donating and withdrawing groups were examined. Yield decreased with the presence of a methoxy substituent in para position on aniline since **3h** was isolated in a moderate 42% yield compared to the unsubstituted *N*-phenyl-1,3-benzothiazol-2-amine **3g** which was obtained in 61% yield. Nonetheless, electron-withdrawing groups on the aromatic ring appeared to be favorable for the reaction except for the formation of **3m** where the presence of a nitro group reduced its solubility, making the purification step more difficult. No steric hindrance was observed when *o*-tolyl isocyanide was used, since **3l** was synthetized in 61% yield. It was noteworthy that the presence of halide substituents (Br, Cl) was also suitable for the reaction which enabled further modifications with transition metal catalysis. Furthermore, a series of functional groups, such as ester (**3j**) and ketone (**3k**) were also tolerated.

Table 1 Optimization of the reaction conditions



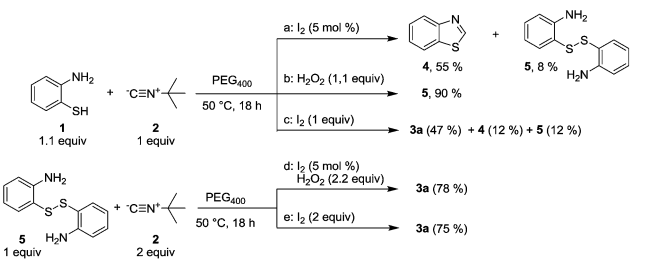

| Entry | Oxidant (equiv.) | Catalyst (equiv.) | Solvent | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $H_2O_2$ (1.1) | $I_2$ (0.05) | $PEG_{400}$ | 89 |
| 2 | DMSO (3.0) | $I_2$ (0.05) | $PEG_{400}$ | Trace[b] |
| 3 | $^tBuOOH$ (1.1) | $I_2$ (0.05) | $PEG_{400}$ | 80 |
| 4 | $K_2S_2O_8$ (1.1) | $I_2$ (0.05) | $PEG_{400}$ | Trace |
| 5 | $H_2O_2$ (1.1) | KI (0.05) | $PEG_{400}$ | 11 |
| 6 | $H_2O_2$ (1.1) | NIS (0.05) | $PEG_{400}$ | 71 |
| 7 | $H_2O_2$ (1.1) | TBAI (0.05) | $PEG_{400}$ | 12 |
| 8 | $H_2O_2$ (1.1) | $I_2$ (0.05) | DCM | 17 |
| 9 | $H_2O_2$ (1.1) | $I_2$ (0.05) | EtOH | 65 |
| 10 | $H_2O_2$ (1.1) | $I_2$ (0.05) | PhMe | 42 |
| 11 | $H_2O_2$ (1.1) | $I_2$ (0.05) | MeCN | 65 |
| 12 | $H_2O_2$ (1.1) | $I_2$ (0.05) | 1,4-Dioxane | 79 |
| 13 | $H_2O_2$ (1.1) | $I_2$ (0.05) | THF | 82 |
| 14 | $H_2O_2$ (1.1) | $I_2$ (0.05) | $H_2O$ | 22 |

[a] The reaction was performed at 135 °C for 24 h. [b] Isolated yields.




Scheme 2 Scope of substrates.

To better understand the overall process, we then focused on the different roles played by the reagents introduced (Scheme 3). A catalytic amount of $I_2$ led mainly to the formation of 1,3-benzothiazole (**4**) in 55% yield, emphasizing the oxidative role of $H_2O_2$ to regenerate the iodine (a). This is in accordance with the result previously observed when the reaction was performed without any metallic catalyst.[11] In addition to 1,3-benzothiazole (**4**), a small amount of 2-[(2-aminophenyl)disulfanyl]aniline (**5**) was also present. This disulfide **5** was next exclusively observed when hydrogen peroxide was used (b). Iodine or hydrogen peroxide is already well known to oxidize thiols into disulfides.[16] Finally, the reactivity was partially recovered when 1 equivalent




Scheme 3 Scope of reaction conditions.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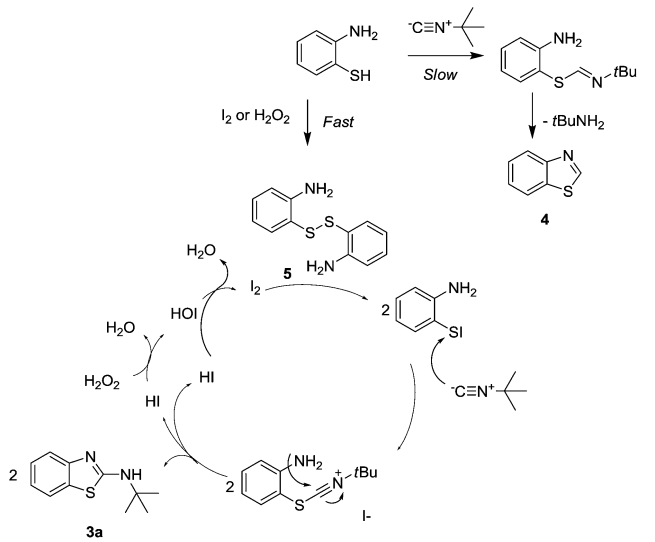


Scheme 4 Plausible mechanism.

of $I_2$ was introduced since **3a** was isolated in 47% yield (c) and the formation of **3a** was significantly improved when the disulfide **5** was directly used as starting material with iodine in catalytic or stoichiometric proportions (d and e).

In the light of these results and those reported in the literature, a plausible mechanism has been proposed (Scheme 4). First, the oxidation step of the thiol into the sulfide **5** occurs faster than the direct condensation of the 2-aminothiophenol with the isocyanide. Then, the resulting disulfide can react with iodine, forming *in situ* the electrophilic sulfenyl iodide. An electrophilic attack on the isocyanide can occur which is followed by the intramolecular attack of the primary amine on the *N*-methylidyne anilinium intermediate. The aromatization process gives the expected product **3a** with the release of hydroiodic acid. Finally, iodine can be regenerated by the oxidation of HI with $H_2O_2$.[16] This reaction appears to be highly atom-economical since water is the only by-product.

# Conclusions

In summary, we have established the possible use of iodine as an efficient catalyst to obtain various substituted 2-aminobenzothiazole derivatives starting from isocyanides and 2-aminothiophenol. This procedure developed in a non-toxic medium offered an eco-friendly alternative to the existing transition-metal catalyst procedure. Furthermore, the regeneration of iodine with hydrogen peroxide highlighted the environmentally sound aspect of the reaction since only water is released as by-product. Various functional groups were tolerated under our conditions, demonstrating the generality of our method.

# Experimental section

### General information

All reagents were purchased from commercial suppliers and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. The infrared spectra of compounds were recorded on a Thermo Scientific Nicolet iS10. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCE II spectrometer at 250 MHz ($^{13}$C, 62.9 MHz) and on a Bruker AVANCE III HD nanobay at 400 MHz ($^{13}$C 101 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) or deuterated solvents (MeOH-$d_4$, $CDCl_3$) as internal standard. The following abbreviations were used for the proton spectra multiplicities: b: broad, s: singlet, d: doublet, t: triplet, q: quartet, p: pentuplet, m: multiplet. Coupling constants ($J$) are reported in Hertz (Hz). High-resolution mass spectra (HRMS (ESI)) were performed on a Maxis Bruker 4G.

### General procedure for the synthesis of benzothiazols (3a–m)

Isocyanide (1.00 mmol) and 2-aminothiophenol (1.10 mmol) were diluted in $PEG_{400}$ (2 mL). Iodine (5 mol%) and an aqueous solution of $H_2O_2$ 35% (96 μL, 1.10 mmol) were next added before heating up to 50 °C for 18 h. After completion the reaction mixture was diluted in $Et_2O$ (10 mL) and a saturated solution of sodium carbonate (10 mL). The aqueous phase was extracted with $Et_2O$ (3 × 5 mL). Then the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel to provide the expected product.

***N*-*tert*-butyl-1,3-benzothiazol-2-amine (3a).**[9b] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3a** was obtained as a white solid (182 mg, 89%). Mp: 93–94 °C (litt 94–96 °C); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.74 (bs, 1H, NH), 7.62 (d, $J$ = 7.4 Hz, 1H), 7.37 (d, $J$ = 8.0 Hz, 1H), 7.19 (t, $J$ = 7.7 Hz, 1H), 6.98 (t, $J$ = 7.6 Hz, 1H), 1.42 (s, 9H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 163.9 (C), 153.0 (C), 130.0 (C), 125.2 (CH), 120.7 (CH), 120.5 (CH), 118.0 (CH), 52.9 (C), 28.5 ($CH_3$).

***N*-*tert*-butyl-5-chloro-1,3-benzothiazol-2-amine (3b).**[9b] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3b** was obtained as a white solid (186 mg, 78%). Mp: 124–125 °C; (litt 119–121 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.51 (d, $J$ = 2.0 Hz, 1H), 7.45 (d, $J$ = 8.4 Hz, 1H), 7.03 (dd, $J$ = 8.3, 2.1 Hz, 1H), 5.15 (s, 1H), 1.50 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 165.8 (C), 153.8 (C), 131.7 (C), 129.1 (C), 121.7 (CH), 121.1 (CH), 119.2 (CH), 53.8 (C), 29.2 ($CH_3$).

***N*-(2,4,4-trimethylpentan-2-yl)-1,3-benzothiazol-2-amine (3c).** Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3c** was obtained as a brown solid (201 mg, 77%). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.0 Hz, 1H), 7.53 (d, $J$ = 8.1 Hz, 1H), 7.27 (t, $J$ = 7.8 Hz, 1H), 7.06 (t, $J$ = 7.6 Hz, 1H), 5.10 (bs, 1H, NH), 1.88 (s, 2H), 1.54 (s, 6H), 1.03 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 164.3 (C), 152.6 (C), 130.8 (C), 125.7 (CH), 121.3 (CH), 120.4 (CH), 119.0 (CH), 57.1 (C), 51.4 (C), 31.7 ($CH_2$), 31.5 ($CH_3$), 29.6 ($CH_3$). HRMS (ESI): $m/z$ $[M + H]^+$ calc. for $C_{15}H_{23}N_3S$ 263.1576, found 263.1575.

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***N*-cyclohexyl-1,3-benzothiazol-2-amine (3d).**[9b] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3d** was obtained as a grey solid (159 mg, 68%). Mp: 108–109 °C (litt 109–110 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57 (d, $J$ = 7.8 Hz, 1H), 7.52 (d, $J$ = 8.1 Hz, 1H), 7.30–7.24 (m, 1H), 7.06 (t, $J$ = 7.6 Hz, 1H), 5.26 (bs, 1H, NH), 3.65–3.51 (m, 1H), 2.19–2.07 (m, 2H), 1.82–1.72 (m, 2H), 1.70–1.59 (m, 1H), 1.51–1.22 (m, 5H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.5 (C), 152.6 (C), 130.4 (C), 125.9 (CH), 121.3 (CH), 120.7 (CH), 118.8 (CH), 54.4 (CH), 33.3 ($CH_2$), 25.5 ($CH_2$), 24.7 ($CH_2$).

***N*-butyl-1,3-benzothiazol-2-amine (3e).**[9b] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3e** was obtained as a white solid (148 mg, 72%). Mp: 84–85 °C (litt 83–84 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (d, $J$ = 7.9 Hz, 1H), 7.53 (d, $J$ = 8.1 Hz, 1H), 7.33–7.25 (m, 1H), 7.08 (t, $J$ = 7.5 Hz, 1H), 5.41 (bs, 1H, NH), 3.43 (t, $J$ = 7.0 Hz, 2H), 1.68 (p, $J$ = 7.1 Hz, 2H), 1.46 (h, $J$ = 7.3 Hz, 2H), 0.98 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.6 (C), 152.6 (C), 130.4 (C), 125.9 (CH), 121.4 (CH), 120.8 (CH), 118.8 (CH), 45.4 ($CH_2$), 31.6 ($CH_2$), 20.0 ($CH_2$), 13.7 ($CH_3$).

***N*-benzyl-1,3-benzothiazol-2-amine (3f).**[17] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3f** was obtained as a beige solid (169 mg, 70%). Mp: 161–162 °C (litt 160–161 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (d, $J$ = 8.0 Hz, 1H), 7.55 (d, $J$ = 8.2 Hz, 1H), 7.43–7.27 (m, 6H), 7.10 (t, $J$ = 7.5 Hz, 1H), 5.60 (s, 1H, NH), 4.65 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.1 (C), 152.4 (C), 137.4 (C), 130.6 (C), 128.8 (CH), 127.9 (CH), 127.7 (CH), 126.0 (CH), 121.8 (CH), 120.8 (CH), 119.1 (CH), 49.4 ($CH_2$).

***N*-phenyl-1,3-benzothiazol-2-amine (3g).**[6b] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3g** was obtained as a white solid (139 mg, 61%). Mp: 156–157 °C (litt 157–159 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.76 (s, 1H, NH), 7.65 (d, $J$ = 7.8 Hz, 1H), 7.60 (d, $J$ = 8.0 Hz, 1H), 7.52 (d, $J$ = 7.8 Hz, 2H), 7.42 (t, $J$ = 7.8 Hz, 2H), 7.34 (t, $J$ = 7.7 Hz, 1H), 7.21–7.14 (m, 2H); $^{13}$C NMR (101 MHz, chloroform-*d*) $\delta$ 164.7 (C), 151.4 (C), 139.9 (C), 129.9 (C), 129.6 (CH), 126.1 (CH), 124.4 (CH), 122.4 (CH), 120.9 (CH), 120.3 (CH), 119.4 (CH).

***N*-(4-methoxyphenyl)-1,3-benzothiazol-2-amine (3h).**[6b] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3h** was obtained as a beige solid (157 mg, 61%). Mp: 160–161 °C (litt 161–162 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.25 (bs, 1H, NH), 7.58 (d, $J$ = 7.8 Hz, 1H), 7.51 (d, $J$ = 8.0 Hz, 1H), 7.41 (d, $J$ = 8.4 Hz, 2H), 7.30 (t, $J$ = 7.7 Hz, 1H), 7.11 (t, $J$ = 7.5 Hz, 1H), 6.96 (d, $J$ = 8.4 Hz, 2H), 3.84 (s, 3H); $^{13}$C NMR (101 MHz, chloroform-*d*) $\delta$ 166.5 (C), 157.3 (C), 151.9 (C), 132.9 (C), 130.1 (C), 126.0 (CH), 123.9 (CH), 122.1 (CH), 120.8 (CH), 119.1 (CH), 114.8 (CH), 55.6 ($CH_3$).

***N*-(4-bromophenyl)-1,3-benzothiazol-2-amine (3i).**[6a] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3i** was obtained as a pale purple solid (189 mg, 75%). Mp: 219–220 °C (litt 217–219 °C); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.60 (s, 1H, NH), 7.82 (d, $J$ = 7.9 Hz, 1H), 7.77 (d, $J$ = 8.7 Hz, 2H), 7.62 (d, $J$ = 8.0 Hz, 1H), 7.53 (d, $J$ = 8.8 Hz, 2H), 7.34 (t, $J$ = 7.7 Hz, 1H), 7.17 (t, $J$ = 7.5 Hz, 1H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 161.2 (C), 151.9 (C), 139.9 (C), 131.7 (CH), 130.0 (C), 125.9 (CH), 122.5 (CH), 121.1 (CH), 119.6 (CH), 119.4 (CH), 113.3 (C).

**Methyl 4-[(1,3-benzothiazol-2-yl)amino]benzoate (3j).**[19] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3j** was obtained as a grey solid (235 mg, 83%). Mp: 209–210 °C (degradation); (litt 204–206 °C); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.90 (bs, 1H, NH), 7.98 (d, $J$ = 8.9 Hz, 2H), 7.92 (d, $J$ = 8.9 Hz, 2H), 7.88 (d, $J$ = 7.9 Hz, 1H), 7.69 (d, $J$ = 7.9 Hz, 1H), 7.38 (td, $J$ = 7.7, 1.3 Hz, 1H), 7.22 (td, $J$ = 7.6, 1.2 Hz, 1H), 3.84 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 165.9 (C), 161.0 (C), 151.7 (C), 144.7 (C), 130.6 (CH), 130.2 (C), 126.0 (CH), 122.8 (CH), 122.5 (C), 121.2 (CH), 119.7 (CH), 117.0 (CH), 51.8 ($CH_3$).

**1-{4-[(1.3-benzothiazol-2-yl)amino]phenyl}ethan-1-one (3k).**[18] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3k** was obtained as a yellow solid (172 mg, 65%). Mp: 190–191 °C; (litt 189–190 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.05 (bs, 1H, NH), 8.01 (d, $J$ = 8.7 Hz, 2H), 7.71 (dd, $J$ = 11.1, 8.0 Hz, 2H), 7.66 (d, $J$ = 8.7 Hz, 2H), 7.40 (ddd, $J$ = 8.3, 7.4, 1.3 Hz, 1H), 7.27 (td, $J$ = 7.3, 1.2 Hz, 1H), 2.60 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 196.8 (C), 161.5 (C), 151.5 (C), 144.1 (C), 132.1 (C), 130.5 (C), 130.4 (CH), 126.6 (CH), 123.5 (CH), 121.1 (CH), 120.5 (CH), 117.6 (CH), 26.6 ($CH_3$).

***N*-(2-methylphenyl)-1,3-benzothiazol-2-amine (3l).**[17] Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3l** was obtained as a brown solid (101 mg, 42%). Mp: 129–130 °C (litt 127–128 °C); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.00 (bs, 1H, NH), 7.67 (d, $J$ = 8.0 Hz, 1H), 7.58 (d, $J$ = 7.9 Hz, 1H), 7.54–7.45 (t, $J$ = 7.0 Hz, 1H), 7.34–7.27 (m, 3H), 7.20 (t, $J$ = 7.5 Hz, 1H), 7.12 (t, $J$ = 7.6 Hz, 1H), 2.36 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 166.4 (C), 151.8 (C), 138.1 (C), 131.8 (C), 131.2 (CH), 130.3 (C), 127.3 (CH), 126.2 (CH), 126.1 (CH), 123.6 (C), 122.1 (CH), 120.9 (CH), 119.1 (CH), 17.9 ($CH_3$).

***N*-(2-methyl-5-nitrophenyl)-1,3-benzothiazol-2-amine (3m).** Following the general procedure and purification: petroleum ether–AcOEt: (8 : 2, v/v), **3m** was obtained as a green solid (82 mg, 58%). Mp: 198–199 °C (degradation); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.92 (bs, 1H, NH), 9.27 (s, 1H), 7.90–7.83 (m, 2H), 7.61 (d, $J$ = 8.0 Hz, 1H), 7.52 (d, $J$ = 8.4 Hz, 1H), 7.35 (t, $J$ = 7.7 Hz, 1H), 7.20 (t, $J$ = 7.6 Hz, 1H), 2.45 (s, 3H); $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 162.5 (C), 151.2 (C), 146.2 (CH), 139.5 (C), 136.0 (C), 131.4 (CH), 130.4 (C), 126.0 (CH), 122.7 (CH), 121.2 (CH), 119.5 (C), 117.6 (CH), 114.7 (CH), 18.5 ($CH_3$). HRMS (ESI): $m/z$ $[M + H]^+$ calc. for $C_{14}H_{12}N_3O_2S$ 286.0644, found 286.0644.

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## Notes and references

1 (*a*) S. J. Hays, M. J. Rice, D. F. Ortwine, G. Johnson, R. D. Schwartz, D. K. Boyd, L. F. Copeland, M. G. Vartanian and P. A. Boxer, *J. Pharm. Sci.*, 1994, **83**, 1425; (*b*) T. Soneda, H. Takeshita, K. Kagoshima, Y. Yamamoto, T. Hosokawa, T. Konosu, N. Masuda, T. Uchida, I. Achiwa, J. Kuroyanagi, T. Fujisawa, A. Yokomizo and T. Noguchi,

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WO2009084614, 2009; (*c*) W. Aelterman, Y. Lang, B. Willemsens, I. Vervest, S. Leurs and F. De Knaep, *Org. Process Res. Dev.*, 2001, **5**, 467; (*d*) D. Fajkusova, M. Pesko, S. Keltosova, J. Guo, Z. Oktabec, M. Vejsova, P. Kollar, A. Coffey, J. Csollei, K. Kralova and J. Jampilek, *Bioorg. Med. Chem.*, 2012, **20**, 7059; (*e*) S. Mishra, K. Monir, S. Mitra and A. Hajra, *Org. Lett.*, 2014, **16**, 6084.

2 P. Jimonet, F. Audiau, M. Barreau, J. C. Blanchard, A. Boireau, Y. Bour, M.-A. Coléno, A. Doble, G. Doeflinger, C. Do Huu, M.-H. Donat, J. M. Duchesne, P. Ganil, C. Guérémy, E. Honoré, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Laduron, J. Le Blevec, M. Meunier, J.-M. Miquet, C. Nemecek, M. Pasquet, O. Piot, J. Pratt, M. Rataud, M. Reibaud, J.-M. Stutzmann and S. Mignani, *J. Med. Chem.*, 1999, **42**, 2828.

3 J. Van Heusden, R. Van Ginckel, H. Bruwiere, P. Moelans, B. Janssen, W. Floren, B. J. Van der Leede, J. Van Dun, G. Sanz, M. Venet, L. Dillen, C. Van Hove, G. Willemsens, M. Janicot and W. Wouters, *Br. J. Cancer*, 2002, **86**, 605.

4 S. Massari, D. Daelemans, M. L. Barreca, A. Knezevich, S. Sabatini, V. Cecchetti, A. Marcello, C. Pannecouque and O. Tabarrini, *J. Med. Chem.*, 2010, **53**, 641.

5 (*a*) N. K. Katari, M. Venkatanarayana and K. Srinivas, *Chem. Sci.*, 2015, **127**, 447; (*b*) S. Vidavalur, M. B. Gajula, R. Tadikonda, M. Nakka, S. Dega, S. K. Yadav and C. Voosala, *Tetrahedron Lett.*, 2014, **55**, 2691.

6 See for instance: (*a*) Z. Zhang, F.-J. Wang, H.-H. Wu and Y.-J. Tan, *Chem. Lett.*, 2015, **44**, 440; (*b*) S. Gaddam, H. R. Kasireddy, K. Konkala, R. Katla and N. Y. V. Durga, *Chin. Chem. Lett.*, 2014, **25**, 732; (*c*) R. Yao, H. Liu, Y. Wu and M. Cai, *Appl. Organomet. Chem.*, 2013, **27**, 109; (*d*) S. K. Sahoo, A. Banerjee, S. Chakraborty and B. K. Patel, *ACS Catal.*, 2012, **2**, 544; (*e*) N. Khatun, J. Jamir, M. Ganesh and B. K. Patel, *RSC Adv.*, 2012, 11557; (*f*) Q. Ding, B. Cao, Q. Yang, X. Liu and Y. Peng, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2011, **186**, 1782; (*g*) Q. Ding, B. Cao, X. Liu, Z. Zong and Y.-Y. Peng, *Green Chem.*, 2010, **12**, 1607; (*h*) Y.-J. Guo, R.-Y. Tang, P. Zhong and J.-H. Li, *Tetrahedron Lett.*, 2010, **51**, 649.

7 See for instance: (*a*) A. Mariappan, K. Rajaguru, S. S. Roja, S. Muthusubramanian and N. Bhuvanesh, *Eur. J. Org. Chem.*, 2016, 302; (*b*) R. Sharma, M. Bala, P. K. Verma and B. Singh, *Synth. Commun.*, 2015, **45**, 2106; (*c*) R. Wang, Z. Chen, L. Yue, W. Pan and J.-J. Zhao, *Tetrahedron Lett.*, 2012, **53**, 4529; (*d*) W. Zhang, Y. Yue, D. Yu, L. Song, Y.-Y. Xu, Y. J. Tian and Y.-J. Guo, *Adv. Synth. Catal.*, 2012, **354**, 2283; (*e*) X. Zhang, X. Jia, J. Wang and X. Fan, *Green Chem.*, 2011, **13**, 413; (*f*) Z.-G. Le, J.-P. Xu, H.-Y. Rao and M. Ying, *J. Heterocycl. Chem.*, 2006, **43**, 1123; (*g*) A. D. Jordan, C. Luo and A. B. Reitz, *J. Org. Chem.*, 2003, **68**, 8693.

8 T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru and E. Ruijter, *Angew. Chem., Int. Ed.*, 2012, **51**, 13058.

9 (*a*) T.-H. Zhu, X.-P. Xu, J.-J. Cao, T.-Q. Wei, S.-Y. Wang and S.-J. Ji, *Adv. Synth. Catal.*, 2014, **356**, 509; (*b*) T.-H. Zhu, S.-Y. Wang, G.-N. Wang and S.-J. Ji, *Chem. Eur. J.*, 2013, **19**, 5850.

10 G.-N. Wang, T.-H. Zhu, S.-Y. Wang, T.-Q. Wei and S.-J. Ji, *Tetrahedron*, 2014, **70**, 8079.

11 V. N. Bochatay, P. J. Boissarie, J. A. Murphy, C. J. Suckling and S. Lang, *J. Org. Chem.*, 2013, **78**, 1471.

12 D. Liu and A. Lei, *Chem.–Asian. J.*, 2015, **10**, 806.

13 M.-A. Hiebel and S. Berteina-Raboin, *Green Chem.*, 2015, **17**, 937.

14 (*a*) J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64; (*b*) E. Colacino, J. Martinez, F. Lamaty, L. S. Patrikeeva, L. L. Khemchyan, V. P. Ananikov and I. P. Beletskaya, *Coord. Chem. Rev.*, 2012, **256**, 2893.

15 (*a*) M.-A. Hiebel, Y. Fall, M.-C. Scherrmann and S. Berteina-Raboin, *Eur. J. Org. Chem.*, 2014, 4643; (*b*) I. Billault, F. Pessel, A. Petit, R. Turgis and M.-C. Scherrmann, *New J. Chem.*, 2015, **39**, 1986; (*c*) R. Turgis, I. Billault, S. Acherar, J. Augé and M.-C. Scherrmann, *Green Chem.*, 2013, **15**, 1016.

16 (*a*) J. Barluenga, M. Marco-Arias, F. González-Bobes, A. Ballesteros and J. M. González, *Chem.–Eur. J.*, 2004, **10**, 1677; (*b*) Å. M. L. Øiestad, A. C. Petersen, V. Bakken, J. Vedde and E. Uggerud, *Angew. Chem., Int. Ed.*, 2001, **40**, 1305.

17 N. Zhao, L. Liu, F. $. Wang, J. Li and W. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 2575.

18 J.-W. Qiu, X.-G. Zhang, R.-Y. Tang, P. Zhong and J.-H. Li, *Adv. Synth. Catal.*, 2009, **351**, 2319.

19 M. A. McGowan, J. L. Henderson and S. L. Buchwald, *Org. Lett.*, 2012, **14**, 1432.