First Synthesis of 3-Amino-2-arylimidazo[1,2-*b*]pyridazines by Groebke–Blackburn Reaction

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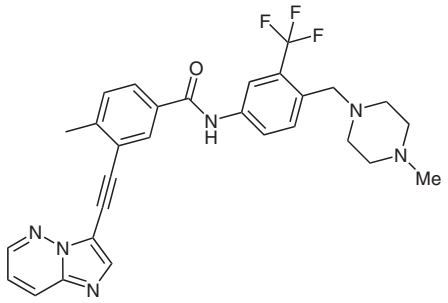
Abstract: The Groebke–Blackburn transformation of an 3-aminopyridazine, a benzaldehyde, and an isocyanide allows the one-step assembly of so far unknown 3-amino-2-arylimidazo[1,2-*b*]-pyridazines. Diversely substituted aldehydes and isocyanides can be used for this reliable three-component condensation, delivering biheterocyclic products with a broad range of different substituents in the imidazole moiety.

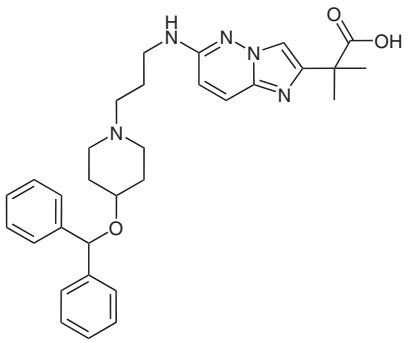
Key words: multicomponent reaction, Groebke–Blackburn reaction, heterocycles, imidazopyridazines, ring closure

In the meantime multicomponent reactions are well-established as a powerful tool for the rapid construction of complex and structurally diverse compounds from relatively simple building blocks.[1] Because of the ubiquitious availability of heterocyclic scaffolds in pharmaceuticals and agrochemicals, the assembly of heterocycles via multicomponent reactions has recently been an emerging field of interest.[2] One of these transformations, the Groebke–Blackburn multicomponent reaction of 2-aminoazines with aldehydes and isocyanides, which delivers fused imidazoazines in a combinatorial, diversity-controlled fashion, is currently in the focus.[3] Although the synthesis of imidazo[1,2-*a*]pyridines,[4–10] imidazo[1,2-*a*]pyrimidines,[6–8,11] imidazo[1,2-*a*]pyrazines,[5–10] imidazo[1,2-*b*]-pyrazoles,[8,9] imidazo[2,1-*b*]thiazoles,[8–10] imidazo[2,1-*b*]-thiadiazoles,[7–9,12] imidazo[1,2-*b*]triazoles,[13] imidazo[1,2-*a*]-benzimidazoles,[9] and imidazo[2,1-*b*]benzothiazoles[6,8,9,14] has been described using this Ugi-type three-component condensation, the transformation of 3-aminopyridazines to imidazo[1,2-*b*]pyridazines has not been reported so far. This is astonishing, because several compounds bearing this bicyclic scaffold show strong biological activities. Ponatinib (**1**) is a potent orally active agent for the treatment of chronic myeloid leukemia,[15] whereas bamirastine (**2**) inhibits the allergic dermal inflammation (Figure 1).[16] Further pharmacologically active imidazo[2,1-*b*]pyridazines are successful inhibitors of malarial kinase,[17] active against human picornaviruses,[18] $GABA_A$ agonists for the treatment of anxiety,[19] or used as ligands for Alzheimer-type β-amyloid plaques.[20]

For a research program we required a concise entry into imidazo[1,2-*b*]pyridazines with a persubstituted imidazole moiety. We realized that the synthesis of such compounds would be possible in only one step using the Groebke–Blackburn methodology. Also other multicomponent condensations, such as the Ugi and the Passerini reactions, have been before successfully applied in crop protection chemistry.[21]



ponatinib (**1**)



bamirastine (**2**)

Figure 1 The pharmacologically active imidazo[2,1-*b*]pyridazine derivatives ponatinib (**1**)[15] and bamirastine (**2**)[16]

The transformation of 3-amino-6-chloropyridazine (**3**) with *tert*-butylisocyanide (**4a**) and benzaldehyde (**5a**) in the presence of ammonium chloride at room temperature gave the trisubstituted imidazo[1,2-*b*]pyridazine **6a** in high yield (Scheme 1).[22] We choose commercially available 3-amino-6-chloropyridazine (**3**) and *tert*-butylisocyanide (**4a**) as starting materials, because the nucleophilic substitution of the chlorine atom would allow an easy entry into imidazo[1,2-*b*]pyridazines with several different substituents in position 6, and the *tert*-butylamine group is readily converted to the free amino function. Ammonium chloride[5a,13,23] proved to be a cheap and efficient acidic promoter with advantages over acetic acid,[3a,4c,11] scandium triflate,[3b,5e,6,10b] perchloric acid,[3c] magnesium chloride,[4b] tin(II) chloride,[4d] *p*-toluenesulfonic acid,[4h,5b]

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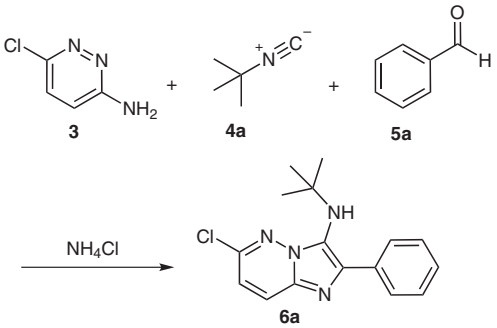
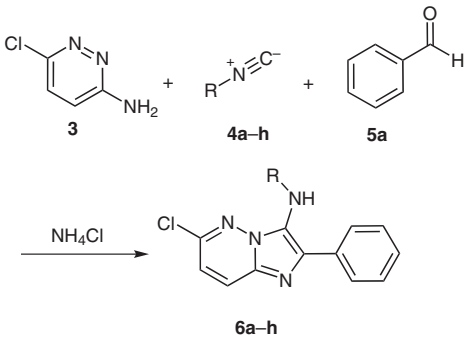
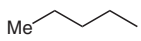
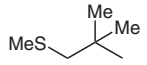
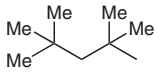
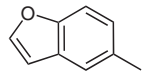
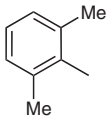
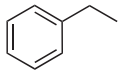
trimethylsilyl chloride,[5c,7,12,14] zirconium(IV) chloride,[8,9,10a] zinc chloride,[4e] cellulose sulfuric acid,[4f] montmorillonite K10,[4e,5d] or the ionic liquid 1-butyl-3-methylimidazolium bromide[4g] which previously have also been used as acidic catalysts in Groebke–Blackburn reactions.



Scheme 1 Groebke–Blackburn-type synthesis of imidazo[1,2-*b*]-pyridazines

Table 1 Synthesis of Imidazo[1,2-*b*]pyridazines with Different Amino Substituents

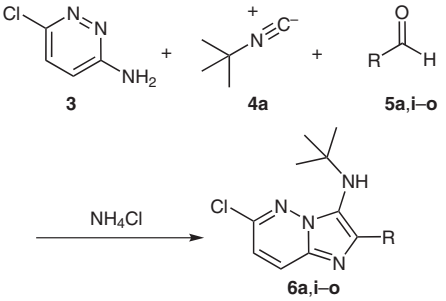


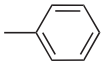
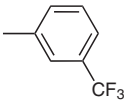
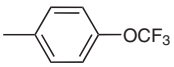
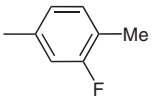
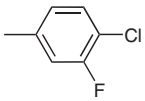
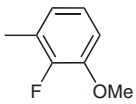
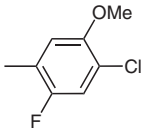
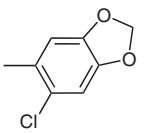
Product **6**	R	Yield (%)	mp (°C)
6a		83	219–222
6b		77	247–249
6c		85	170–172
6d		58	128–132
6e		92	141–144
6f		60	254–256
6g		67	115–117
6h		86	137–140

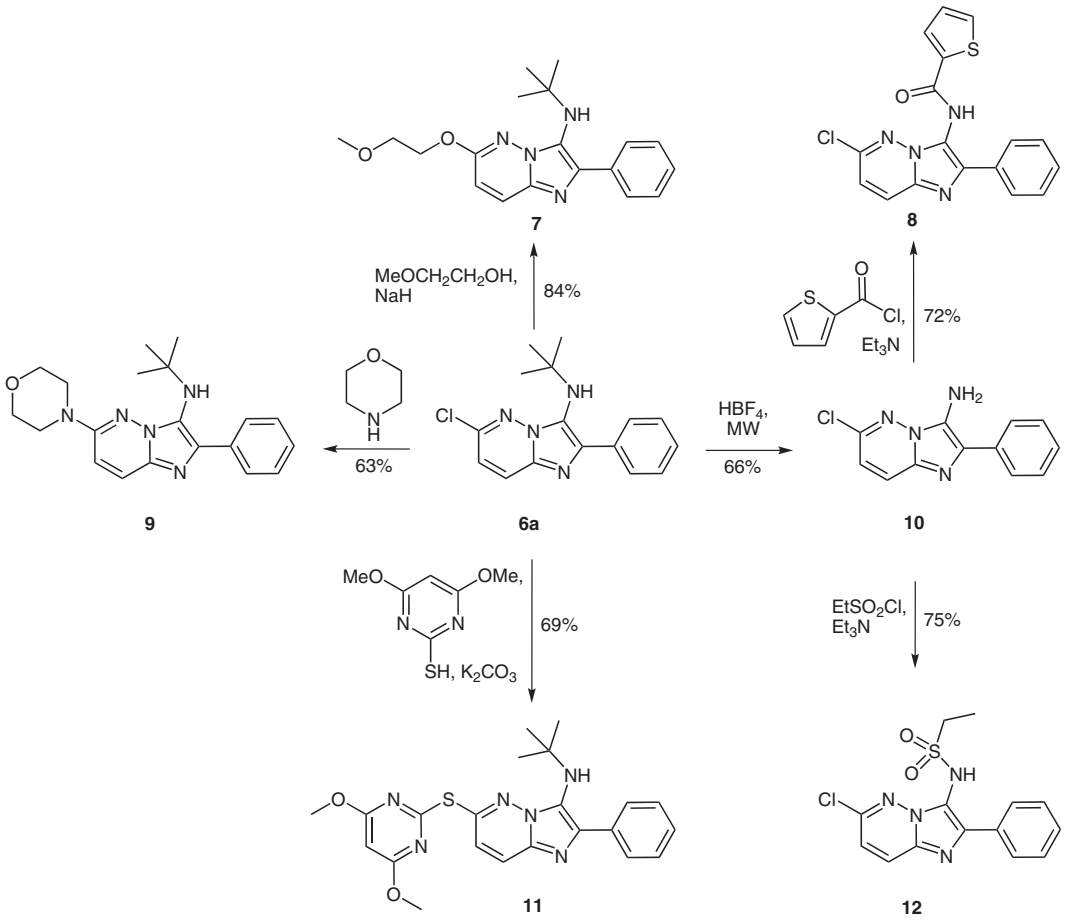
There seems to be a huge scope regarding variability of the applied isocyanide. We obtained good results with both aliphatic and aromatic isonitriles. The aliphatic isocyanides can be of primary or tertiary nature (Table 1).

Also the substitution pattern of the benzaldehyde seems to be broadly variable, because there is no major yield difference between benzaldehydes with *ortho*, *meta*, and *para* substituents. In addition both electron-donating and electron-withdrawing groups have been applied without any difficulties (Table 2). As also aliphatic[3,4e,5d],e[7–9,10a] as well as heteroaromatic[3c,4c–g,5b,6,8–10] aldehydes have been successfully used in the Groebke–Blackburn reaction, also such substrates should be applicable without problems.

Table 2 Synthesis of Imidazo[1,2-*b*]pyridazines with Different Substituents in the Phenyl Ring



Compd **6**	R	Yield (%)	mp (°C)
6a		83	219–222
6i		90	115–118
6j		79	172–175
6k		92	165–168
6l		66	117–120
6m		81	85–87
6n		74	126–127
6o		93	211–214



Scheme 2 Different transformations of the imidazo[1,2-*b*]pyridazine **6a**

3-*tert*-Butylamino-6-chloro-2-phenylimidazo[1,2-*b*]pyridazine (**6a**) can be easily transformed into further novel analogues, mainly due to the leaving-group character of its chloro function. Some possible derivatizations are the nucleophilic substitution with amines, alkoxides, and thiolates, delivering the target compounds **7**, **9**, and **11**. Furthermore, the alkyl amine could be cleaved to a free amino function by de-*tert*-butylation with aqueous fluoroboric acid under microwave irradiation.[10a] The resulting primary amine **10** can be easily acylated and sulfonylated, respectively, to obtain the amide **8** and the sulfonamide **12**[24] (Scheme 2).

In conclusion, we have achieved the first synthesis of 3-amino-2-aryl-6-chloroimidazo[1,2-*b*]pyridazines by Groebke–Blackburn reaction. Several different isocyanides and benzaldehydes could be applied to this three-component condensation, delivering biheterocycles with a broad variety of substituents in the imidazole moiety. The chloro atom in the pyridazine part can be easily replaced through various nucleophilic substitutions, it is also easily possible to further functionalize the amino group.

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(22) **Representative Procedure**
tert-Butyl isocyanide (**4a**, 200 mg, 2.4 mmol), benzaldehyde (**5a**, 233 mg, 2.2 mmol), and 3-amino-6-chloropyridazine (**3**, 260 mg, 2.0 mmo) are consecutively added to a solution of NH_4Cl (107 mg, 2.0 mmol) in MeOH (10 mL). The reaction mixture is stirred for 16 h at r.t. Subsequently, the solvent was removed in vacuo and the remainder taken up in EtOAc. This organic layer was washed with brine and H_2O, dried over Na_2SO_4 and evaporated. The residue was purified either by crystallization from Et_2O or by chromatography on silica gel, using cyclohexane–EtOAc (4:1) as eluent to deliver 3-*tert*-butylamino-6-chloro-2-phenylimidazo[1,2-*b*]pyridazine as yellow crystals (**6a**, 500 mg, 1.7 mmol, 83%); mp 219–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 9 H), 3.44 (br s, 1 H), 6.95 (d, 1 H), 7.32 (t, 1 H), 7.43 (t, 2 H), 7.80 (d, 1 H), 8.22 (d, 2 H) ppm. LC-MS: t_R = 1.93 min, *m/z* = 301 [M + 1].

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(24) **Further Spectroscopic Data**
Compound **6b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, 3 H), 1.38 (q, 2 H), 1.57 (q, 2 H), 3.15 (q, 2 H), 3.99 (t, 1 H), 6.85 (d, 1 H), 7.32 (t, 1 H), 7.44 (t, 2 H), 7.78 (d, 1 H), 8.03 (d, 2 H) ppm. LC-MS: t_R = 2.05 min, *m/z* = 301 [M + 1].
Compound **6c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.89 (m, 10 H), 3.22 (q, 1 H), 3.89 (d, 1 H), 6.87 (d, 1 H), 7.32 (t, 1 H), 7.44 (t, 2 H), 7.78 (d, 1 H), 8.10 (d, 2 H) ppm. LC-MS: t_R = 2.15 min, *m/z* = 327 [M + 1].
Compound **6d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 6 H), 2.20 (s, 3 H), 2.73 (s, 2 H), 3.96 (br s, 1 H), 6.96 (d, 1 H), 7.33 (t, 1 H), 7.42 (t, 2 H), 7.80 (d, 1 H), 8.21 (d, 2 H) ppm. LC-MS: t_R = 2.04 min, *m/z* = 347 [M + 1].
Compound **6e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 6 H), 1.10 (s, 9 H), 1.18 (s, 2 H), 3.56 (br s, 1 H), 6.91 (d, 1 H), 7.31 (t, 1 H), 7.42 (t, 2 H), 7.78 (d, 1 H), 8.17 (d, 2 H) ppm. LC-MS: t_R = 2.32 min, *m/z* = 357 [M + 1].
Compound **6f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.88 (br s, 1 H), 6.55 (d, 1 H), 6.64 (s, 1 H), 6.72–6.79 (m, 2 H), 7.05 (d, 1 H), 7.29–7.56 (m, 4 H), 7.91 (d, 1 H), 8.10 (d, 2 H) ppm. LC-MS: t_R = 1.89 min, *m/z* = 361 [M + 1].
Compound **6g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01 (s, 6 H), 5.69 (br s, 1 H), 6.81–6.93 (m, 4 H), 7.14–7.20 (m, 3 H), 7.58 (dd, 2 H), 7.82 (d, 1 H) ppm. LC-MS: t_R = 2.03 min, *m/z* = 349 [M + 1].
Compound **6h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30–4.39 (m, 3 H), 6.87 (d, 1 H), 7.19–7.36 (m, 6 H), 7.47 (t, 2 H), 7.78 (d, 1 H), 8.01 (d, 2 H) ppm. LC-MS: t_R = 1.98 min, *m/z* = 335 [M + 1].
Compound **6i**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 9 H), 3.46 (br s, 1 H), 6.99 (d, 1 H), 7.52–7.83 (m, 4 H), 8.47 (d, 1 H), 8.66 (d, 1 H) ppm. LC-MS: t_R = 2.19 min, *m/z* = 369 [M + 1].

Compound **6j**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 3.43 (br s, 1 H), 6.97 (d, 1 H), 7.21–7.28 (m, 2 H), 7.80 (d, 1 H), 8.30 (d, 2 H) ppm. LC-MS: t_R = 2.20 min, *m/z* = 385 [M + 1].
Compound **6k**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 9 H), 2.31 (s, 3 H), 3.40 (br s, 1 H), 6.95 (d, 1 H), 7.22 (t, 1 H), 7.79 (d, 1 H), 7.92–7.98 (m, 2 H) ppm. LC-MS: t_R = 2.14 min, *m/z* = 333 [M + 1].
Compound **6l**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 9 H), 3.42 (br s, 1 H), 6.98 (d, 1 H), 7.43 (t, 1 H), 7.80 (d, 1 H), 8.03 (d, 1 H), 8.15 (d, 1 H) ppm. LC-MS: t_R = 2.23 min, *m/z* = 353 [M + 1].
Compound **6m**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H), 3.58 (br s, 1 H), 3.95 (s, 3 H), 6.88–7.04 (m, 2 H), 7.20 (t, 1 H), 7.39 (t, 1 H), 7.82 (d, 1 H) ppm. LC-MS: t_R = 1.92 min, *m/z* = 349 [M + 1].
Compound **6n**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 9 H), 3.58 (br s, 1 H), 3.96 (s, 3 H), 7.00 (d, 1 H), 7.27 (s, 1 H), 7.48 (d, 1 H), 7.83 (d, 1 H) ppm. LC-MS: t_R = 2.07 min, *m/z* = 383 [M + 1].
Compound **6o**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H), 3.49 (br s, 1 H), 6.03 (s, 2 H), 6.95–7.00 (m, 2 H), 7.06 (s, 1 H), 7.81 (d, 1 H) ppm. LC-MS: t_R = 1.98 min, *m/z* = 379 [M + 1].

Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 3.33 (br s, 1 H), 3.48 (s, 3 H), 3.80 (t, 2 H), 4.49 (t, 2 H), 6.63 (d, 1 H), 7.28 (t, 1 H), 7.41 (t, 2 H), 7.72 (d, 1 H), 8.23 (d, 2 H) ppm. LC-MS: t_R = 1.58 min, *m/z* = 341 [M + 1].
Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (br s, 1 H), 7,11 (dd, 1 H), 6.95 (d, 1 H), 7.33 (t, 1 H), 7.45 (t, 2 H), 7.82–7.88 (m, 2 H), 7.97 (d, 1 H), 8.22 (d, 2 H) ppm. LC-MS: t_R = 1.89 min, *m/z* = 355 [M + 1].
Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 9 H), 3.45 (t, 4 H), 3.72 (t, 4 H), 3.51 (br s, 1 H), 6.89 (d, 1 H), 7.31 (t, 1 H), 7.43 (t, 2 H), 7.82 (d, 1 H), 8.26 (d, 2 H) ppm. LC-MS: t_R = 1.77 min, *m/z* = 352 [M + 1].
Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (br s, 2 H), 6.83 (t, 1 H), 7.32 (t, 1 H), 7.40–7.52 (m, 2 H), 7.76 (t, 1 H), 7.92 (t, 2 H) ppm. LC-MS: t_R = 1.46 min, *m/z* = 245 [M + 1].
Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 9 H), 3.56 (br s, 1 H), 3.77 (s, 6 H), 5.80 (s, 1 H), 7.31 (t, 2 H), 7.44 (t, 2 H), 7.82 (d, 1 H), 8.29 (d, 2 H) ppm. LC-MS: t_R = 2.12 min, *m/z* = 437 [M + 1].
Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, 3 H), 2.74 (q, 2 H), 3.56 (br s, 1 H), 6.97 (d, 1 H), 7.33 (t, 1 H), 7.40–7.48 (m, 2 H), 7.80 (d, 1 H), 8.30 (d, 2 H) ppm. LC-MS: t_R = 1.67 min, *m/z* = 337 [M + 1].