RSC Advances



PAPER

View Article Online
View Journal | View Issue



Cite this: RSC Adv., 2021, 11, 22710

Synthesis of indazoles from 2-formylphenylboronic acids†

A method for the synthesis of indazoles was developed which involves a copper(II) acetate catalysed reaction of 2-formylboronic acids with diazadicaboxylates followed by acid or base induced ring closure. Hydrazine dicarboxylates were also shown as competent reaction partners for the synthesis of indazoles, however, they required a stoichiometric amount of copper(III) acetate for the C-N bond formation step. The transformation can be efficiently performed as a two step-one pot procedure to give a range of 1*N*-alkoxycarbonyl indazoles.

Received 24th May 2021 Accepted 22nd June 2021

DOI: 10.1039/d1ra04056a

rsc.li/rsc-advances

Introduction

The indazole motif plays an important role in pharmaceutically relevant compounds including drugs and candidate drugs *e.g.* Lonidamine, Gamendazole, Bendazac, Pazopanib, Axitinib (Fig. 1).¹⁻⁴ A number of approaches have been developed to assemble indazole from 2-aminotoluenes,⁵ 2-acyl-halobenzenes,⁶⁻⁸ 2-aminophenyloximes,⁹ and 2-nitrobenzaldehydes,^{10,11} and by [3 + 2] annulations of *in situ* generated arynes.¹²⁻¹⁴ Most of the above mentioned methods lead to the defined 1*N* or 2*N* indazole substitution pattern, however, they require harsh conditions or long routes to the key intermediates limiting their application. Selective *N*-functionalization of indazoles has been reported for alkylation reactions¹⁵⁻¹⁷ and few reports can be found on selective *N*-acylation of indazoles.¹⁸

Previously, we demonstrated the construction of amino-quinazolines from 2-formylphenylboronic acids. ¹⁹ This method involved the Chan–Evans–Lam reaction for the C–N bond formation. To extend this approach for the synthesis of indazoles, we turned our attention to copper catalysed addition of phenyl boronic acids to azodicarboxylates reported by Uemura and Chatani. ²⁰ Using 2-formylphenylboronic acids 1 as substrates, the addition to N—N bond in azadicarboxylates 2 would give *N*-arylhydrazine intermediates 3 which could be further transformed to indazoles 4 and 5 (Scheme 1).

Results and discussion

The initial investigation of the arylation conditions was performed for the reaction of 2-formylphenylboronic acid (1a) with diethylazodicarboxylate (DEAD, 2a) using Cu(OAc)₂ as a catalyst in a range of solvents (Table 1, entries 1–9). Solvents such as MeCN, DMF and DMA were found to be appropriate to obtain the product 3a together with its cyclic tautomer 6a in a good yield (Table 1, entries 5 and 6). Decreased catalyst loading was also possible using DMA as a solvent without affecting the product 6a yield (Table 1, entries 7–9). Range of other copper sources was investigated (Table 1, entries 10–14). CuCl₂ Cu(OTf)₂ Cu(acac)₂ performed as efficient catalysts for C-N bond formation giving the product 3a in high yield (Table 1, entries 10–12). Copper(i) source such as CuCl proved to be ineffective catalyst, while catalytic amount of CuI enabled product 3a formation in good yield (Table 1, entries 13 and 14).

Next, the conditions were investigated for the indazole ring closure using arylhydrazine 3a (Table 2). Acidic reaction conditions enabled the condensation of arylhydrazine 3a to 1*N*-etoxycarbonyl indazole (4a) (Table 2, entries 1–5). TFA in DCM and in MeCN gave the expected product 4a in good yield (Table 2, entries 1 and 2). Neat AcOH at r. t. did not enable the cyclization of arylhydrazine 3a, while heating in a solution of MeCN induced formation of indazole 4a (Table 2, entries 3 and 4).

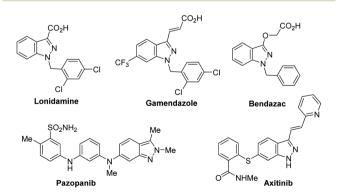


Fig. 1 Indazole containing drugs (Lonidamine, Gamendazole, Bendazoc, Pazopanib) and candidate drug (Axitinib).

^aLatvian Institute of Organic Synthesis, Aizkraukles 21, Riga, LV-1006, Latvia. E-mail: aigars@osi.lv

^bFaculty of Materials Science and Applied Chemistry, Riga Technical University, P. Valdena Str. 3, Riga, LV-1048, Latvia

[†] Electronic supplementary information (ESI) available. See DOI 10.1039/d1ra04056a

$$R^{1}O \xrightarrow{N=N} OR^{1}$$

$$R \xrightarrow{Q} Cat. Cu(II)$$

$$R \xrightarrow{Q} R^{1}OR^{1}$$

$$R \xrightarrow{Q} R^{1}OR^{1}$$

$$R^{2} = R^{1}O(C=0)$$

$$R^{2}OR^{1}$$

$$R^{2} = R^{1}O(C=0)$$

Scheme 1 Indazole synthesis from 2-formylphenylboronic acids.

Formic acid was strong enough to enable the formation of indazole 4a at room temperature in a solution of MeCN (Table 2, entry 5).

The use of a base in alcoholic solvent provided unprotected indazole 5a (Table 2, entries 6–8). Both K_2CO_3 and KOH could be efficiently used for the ring closure – deacylation reaction of arvlhydrazine 3a.

Next, the one pot formation of 1*N*-etoxycarbonyl indazole (4a) from 2-formylphenylboronic acid (1a) was investigated (Table 3). Unfortunately, DMA which was the solvent of choice for high yielding arylation of DEAD was not suitable for the ring closure step in the presence of TFA (Table 3, entry 1). In this case, the arylhydrazine 3a intermediate was not transformed to product 4a, according to LC-MS. In turn, the addition of TFA in DCM in an amount to sufficiently dilute DMA, enabled the formation of expected product 4a in a good yield (Table 3, entry 2). The use of DCM as a solvent for both steps was less productive (Table 3, entry 3). However, MeCN was found as an appropriate solvent for both arylation and ring closure in the presence of TFA to give 1*N*-protected indazole 4a in a good overall yield (Table 3, entry 4).

Table 1 Conditions for the arylation of DEAD (2a)

Entry	Copper catalyst	Solvent	Isolated yield
1	20 mol% Cu(OAc) ₂	$MeOH^a$	0%
2	20 mol% Cu(OAc) ₂	PhMe	0%
3	20 mol% Cu(OAc) ₂	THF	64%
4	20 mol% Cu(OAc) ₂	MeCN	80%
5	20 mol% Cu(OAc) ₂	DMF^b	83%
6	20 mol% Cu(OAc) ₂	\mathbf{DMA}^c	98%
7	15 mol% Cu(OAc) ₂	DMA^c	98%
8	10 mol% Cu(OAc) ₂	DMA^c	98%
9	5 mol% Cu(OAc) ₂	DMA^c	96%
10	10 mol% CuCl ₂	DMAc	94%
11	10 mol% Cu(OTf) ₂	DMAc	99%
12	10 mol% Cu(acac) ₂	DMAc	97%
13	10 mol% CuCl	DMAc	25%
14	10 mol% CuI	DMAc	93%

^a Violent DEAD decomposition observed. ^b N,N-Dimethylformamide.

^c N,N-Dimethylacetamide.

Table 2 Cyclization of arylhydrazone 3a to indazoles 4a and 5a

Entry	Reagent	Solvent	Temp., time	Product	Yield
1 2	5 equiv. TFA 5 equiv. TFA	DCM MeCN	25 °C, 12 h 25 °C, 12 h	4a 4a	63% 64%
3 4	AcOH 30 equiv. AcOH	Neat MeCN	r. t., 12 h 70 °C, 12 h	4a 4a	0% 56%
5 6 7	30 equiv HCOOH 3 equiv. K ₂ CO ₃ 3 equiv. K ₂ CO ₃	MeCN MeOH MeOH	r. t., 12 h 70 °C, 1 h 25 °C, 12 h	4a 5a 5a	56% 67% 67%
8	4 equiv. KOH	EtOH	r. t., 12 h	5a	59%

With one-pot conditions in hand, the synthesis of other alkoxycarbonylindazoles **4b–d** was performed by the reaction of boronic acid **1a** with azodicarboxylates **2b–d** (Table 4). The best yield of product **4b** was obtained with diisopropyl azodicarboxylate (DIAD, **2b**, Table 4, entry 1).

The scope of boronic acid substitution was investigated in the reaction of a range of formylboronic acids **1b-f** with DIAD (**2b**) followed by cyclization (Scheme 2). Substrates **1b-d** bearing methoxy and benzyloxy groups provided indazoles **4e-g** in a good to moderate yield. In the case of substrates **1e,f** bearing electronwithdrawing substituents, yields of products **4h, i** were decreased.

Thiophene boronic acid 8 was found a suitable substrate to obtain thienopyrazole derivative 9 in a good yield (Scheme 3).

Hydrazine dicarboxylate 7a was also explored as a reagent for the synthesis of indazoles instead of azodicarboxylate 2a (Table 5). 2-Formylphenylboronic acid (1a) was subjected to the reaction with diethyl hydrazine dicarboxylate (7a) using the two-step one-pot procedure for the formation of indazole 4a. The catalytic amount of $Cu(OAc)_2$ and excess of triethylamine was not sufficient to achieve good yield of product 4a formation (Table 5, entry 1). The use of equimolar amount of $Cu(OAc)_2$ and an

Table 3 One-pot conversion of boronic acid 1a to indazole 4a

Entry	Solvent	Conditions, step 2	3a, isolated yield
1	DMA	10 equiv. TFA, 25 °C, 2 h	0%
2	DMA	TFA: DCM 1: 4^a , 25 °C, 2 h	73%
3	DCM	5 equiv. TFA, 25 °C, 1 h	48%
4	MeCN	5 equiv. TFA, 25 $^{\circ}$ C, 1 h	78%

^a 3 mL of TFA/DCM mixture added per 1 mL of DMA.

Table 4 Azodicarboxylate 2 scope for the synthesis of indazoles 4

Entry	R	4, isolated yield
1	<i>i</i> -Pr	4b , 86%
2	Bn	4c , 60%
3	<i>i</i> -Bu	4d , 45%

Scheme 2 The reaction of substituted formylboronic acids with DIAD (2b).

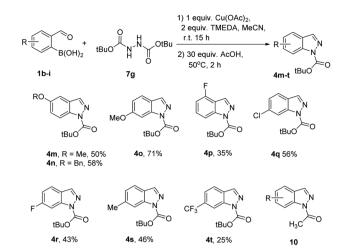
Scheme 3 The reaction of substituted formylboronic acids with DIAD (2b).

excess of triethylamine for the first step enabled good yield of product **4a** over two steps, while increasing the amount of Cu(OAc)₂ reduced the yield of product **4a** (Table 5, entries 2 and

Table 5 Synthesis of indazole using of hydrazine dicarboxylate 7a

Entry	Catalyst	Solvent	Additive	NMR yield ^a
1	20 mol% Cu(OAc) ₂	MeCN	3 equiv. TEA	25%
2	1 equiv. Cu(OAc) ₂	MeCN	3 equiv. TEA	66%
3	1.5 equiv. Cu(OAc) ₂	MeCN	3 equiv. TEA	50%
4	1 equiv. Cu(OAc) ₂	MeCN	None	26%
5	1 equiv. Cu(OAc) ₂	MeCN	2 equiv. TMEDA	67%
6	1 equiv. Cu(OAc) ₂	MeCN	3 equiv. DIPEA	60%
7	1 equiv. CuCl	MeCN	3 equiv. TEA	35%
8	1 equiv. CuCl ₂	MeCN	3 equiv. TEA	25%

^a NMR yield, using 1,3,5-trimethoxybenzene as internal standard.



Scheme 4 Scope of boronic acids 1 in the reaction with dia-zadicarboxylate 7g.

3). The transformation of 2-formylphenylboronic (1a) to indazole 4a was not efficient in the absence of base for the first step, however, TEA could be replaced by TMEDA and DIPEA without significantly reducing the product 4b yield (Table 5, entries 5 and 6). Several other Cu salts were tried for the first step of indazole 4b formation, however, were found to be ineffective (Table 5, entries 7 and 8). The need for an equimolar amount of Cu (OAc)₂ for successful synthesis of indazole 4a using hydrazine dicarboxylate 7a implies *in situ* oxidation of reagent 7a to azodicarboxylate 2a (see also Scheme 5). However, C-N bond formation with hydrazine dicarboxylate 7a in the Chan-Evans-Lam reaction cannot be excluded.²¹

Next, a range of hydrazine dicarboxylates **7a–g** was explored as reaction components for a one-pot two-step synthesis of indazoles **4a–d**, **j–l** (Table 6). TFA was a suitable acid for the cyclization step to give the corresponding products **4a–d**, **j**, **k** from the reaction of boronic acid **1a** with hydrazine dicarboxylates **7a–f** (Table 6, entries 1–6). For the synthesis of product **4l** bearing acid labile *t*-Bu group, acetic acid at elevated temperature was used instead of TFA (Table 6, entry 7). This approach successfully provided product **4l** in a very good yield (Table 6, entry 8).

The scope of phenyl boronic acids 1b-i was explored with di*tert*-butyl hydrazine dicarboxylate 7g as a reaction component

Scheme 5 Proposed mechanism for the C-N bond forming step.

Table 6 Hydrazine dicarboxylate 7 scope for the synthesis of indazoles 4

Entry	7, R	Acid	4, isolated yield
1	7a , Et	TFA	4a , 63%
2	7 b , <i>i</i> -Pr	TFA	4b , 47%
3	7 c , Bn	TFA	4c , 46%
4	7 d , <i>i</i> -Bu	TFA	4d , 61%
5	7 e , Me	TFA	4j , 63%
6	7 f , allyl	TFA	4k, 40%
7	7 g , <i>t</i> -Bu	AcOH	4l , 73%

$$3a \longrightarrow \begin{pmatrix} OH \\ -H_2O \\ \hline \\ -CO_2 \\ -EIOH \\ -H\oplus \\ \hline \\ -H_2O \\ \hline \\ -Base \\ -MeOC(=O)OEt \\ \hline \\ \\ H \\ \hline \end{pmatrix} \rightarrow \begin{pmatrix} OH \\ -H_2O \\ -CO_2 \\ -EIOH \\ -H\oplus \\ \hline \\ -H_2O \\ -EIOH \\ -H\oplus \\ \hline \\ -H_2O \\$$

Scheme 6 Proposed mechanism for the condensation step

for the synthesis of 1*N*-Boc indazoles **4m–t** (Scheme 4). The major reason for reduction was formation of *N*-acetyl indazoles **10** as by-products (see ESI \dagger for the characterization of **10a**, R = H).

The mechanism for the C-N bond formation in the copper catalysed reaction of arylboronic acids with diazadicarboxylates has been proposed by Uemura and Chatani. ²⁰ According to this, the transmetalation reaction of arylboronic acid **1a** with a copper catalyst would form an arylcopper species **10** (Scheme 5). Addition of intermediate **10** to N=N double bond gives an arylhydrazine **11** which undergoes the transmetalation with boronic acid **1a** to give intermediate **12** and return arylcopper species **10** into catalytic cycle. Work-up would produce arylhydrazine **3a**. Noteworthy, it was shown by Uemura and Chatani that dialkoxycarbonyl hydrazines are not competent substrates for this reaction unless additional oxidant is added. ²⁰ This implies that hydrazine **7a** is likely oxidised to diazadicarboxylate **2a** by stoichiometric amount of copper source.

The proposed mechanism for the condensation of arylhydrazine intermediate into indazole is given in Scheme 6. In the presence of acid, *N*-acyliminium ion 13 is formed. Selective hydrolytic cleavage of one ethoxycarbonyl group in intermediate 13 gives 1*N*-ethoxycarbonyl indazole 4a. In turn, basic conditions would enable cleavage of both ethoxycarbonyl groups leading to intermediate 14 which eliminates water to give indazole 5a.

Conclusions

In summary, copper catalysed reaction of 2-formylboronic acids with diazadicaboxylates followed by acid or base induced ring closure is a convenient method for the synthesis of 1*N*-alkoxycarbonyl indazole derivatives. The indazole synthesis can also be performed using hydrazine dicarboxylates as reaction partners for the synthesis of indazoles, however, required a stoichiometric amount of copper(II) acetate for the C–N bond formation step. The method is based on readily available building blocks and can be performed at relatively mild reaction conditions which enables its application for the synthesis of indazole motif containing compounds.

Author contributions

V. S. and A. S performed the synthesis. A. J. wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Funding from H2020 MSC-ITN project CARTNET "Combating Antimicrobial Resistance Training Network", grant agreement ID: 765147 is acknowledged.

Notes and references

- K. B. Goodman, H. Cui, S. E. Dowdell, D. E. Gaitanopoulos,
 R. L. Ivy, C. A. Sehon, R. A. Stavenger, G. Z. Wang,
 A. Q. Viet, W. Xu, G. Ye, S. F. Semus, C. Evans, H. E. Fries,
 L. J. Jolivette, R. B. Kirkpatrick, E. Dul, S. S. Khandekar,
 T. Yi, D. K. Jung, L. L. Wright, G. K. Smith, D. J. Behm,
 R. Bentley, C. P. Doe, E. Hu and D. Lee, *J. Med. Chem.*,
 2007, 50, 6–9.
- 2 Y. Hu, D. Cole, R. A. Denny, D. R. Anderson, M. Ipek, Y. Ni, X. Wang, S. Thaisrivongs, T. Chamberlain, J. P. Hall, J. Liu, M. Luong, L.-L. Lin, J.-B. Telliez and A. Gopalsamy, *Bioorg. Med. Chem. Lett.*, 2011, 21, 4758–4761.
- 3 J. Schoene, T. Gazzi, P. Lindemann, M. Christmann, A. Volkamer and M. Nazaré, *ChemMedChem*, 2019, 14, 1514–1527.
- 4 S.-G. Zhang, C.-G. Liang and W.-H. Zhang, *Molecules*, 2018, 23, 2783.
- 5 J.-H. Sun, C. A. Teleha, J.-S. Yan, J. D. Rodgers and D. A. Nugiel, J. Org. Chem., 1997, 62, 5627–5629.
- 6 X. Xiong, Y. Jiang and D. Ma, Org. Lett., 2012, 14, 2552-2555.
- 7 E. Dubost, S. Stiebing, T. Ferrary, T. Cailly, F. Fabis and V. Collot, *Tetrahedron*, 2014, 70, 8413–8418.
- 8 K. Lukin, M. C. Hsu, D. Fernando and M. R. Leanna, *J. Org. Chem.*, 2006, **71**, 8166–8172.
- 9 B. C. Wray and J. P. Stambuli, Org. Lett., 2010, 12, 4576-4579.
- J. Schoene, H. Bel Abed, P. Schmieder, M. Christmann and M. Nazaré, *Chem.-Eur. J.*, 2018, 24, 9090–9100.

- 11 H. Bel Abed, N. Weißing, J. Schoene, J. Paulus, N. Sewald and M. Nazaré, *Tetrahedron Lett.*, 2018, **59**, 1813–1815.
- 12 G. Chen, M. Hu and Y. Peng, *J. Org. Chem.*, 2018, **83**, 1591–1597.
- 13 Z. Liu, F. Shi, P. D. G. Martinez, C. Raminelli and R. C. Larock, *J. Org. Chem.*, 2008, 73, 219–226.
- 14 P. Li, C. Wu, J. Zhao, D. C. Rogness and F. Shi, *J. Org. Chem.*, 2012, 77, 3149–3158.
- 15 K. W. Hunt, D. A. Moreno, N. Suiter, C. T. Clark and G. Kim, *Org. Lett.*, 2009, **11**, 5054–5057.
- 16 M. Cheung, A. Boloor and J. A. Stafford, J. Org. Chem., 2003, 68, 4093–4095.
- 17 G. Luo, L. Chen and G. Dubowchik, *J. Org. Chem.*, 2006, 71, 5392–5395.
- 18 D. M. M. M. Dissanayake and A. K. Vannucci, *Org. Lett.*, 2019, 21, 457–460.
- 19 V. Solomin, A. Seins and A. Jirgensons, Synlett, 2020, 31.
- 20 T. Uemura and N. Chatani, *J. Org. Chem.*, 2005, **70**, 8631–8634.
- 21 L. Raus, O. Tsubrik and U. Maeorg, *Proc. Est. Acad. Sci. Chem.*, 2005, **54**, 12.