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Synthesis of p38 MAP kinase inhibitor BIRB 796 and analogs via copper-mediated N-arylation reaction

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ABSTRACT

Direct N-arylation of urea (**5**) with various arylboronic acids mediated by cupric acetate furnished BIRB796 and a range of N-substituted BIRB796 analogs in good to moderate yields in one step. Urea (**5**) was readily synthesized from commercially available compounds.

1. Introduction

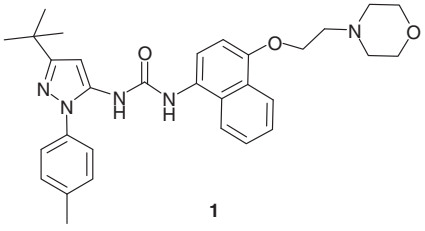
BIRB796 (**1**, Fig. 1) is the first urea-based small molecule p38 MAP kinase inhibitor from Boehringer Ingelheim that has advanced as a clinical candidate for the treatment of inflammatory diseases.[1] The synthesis of BIRB796 and its derivatives is still being actively studied in several research laboratories.[2]

The key step of previous syntheses of BIRB796 involved the formation of the urea bond through the reactions of isocyanates[3] or carbamates[4] with amines.

For example, the original synthesis of BIRB796 involved the use of phosgene to generate isocyanate in situ, which would require special equipment for industrial scale synthesis (Scheme 1).

A scalable synthesis of BIRB796 was later developed through carbamate **4** generated from amine **3** using trichloroethyl chloroformate (Scheme 2).[5]

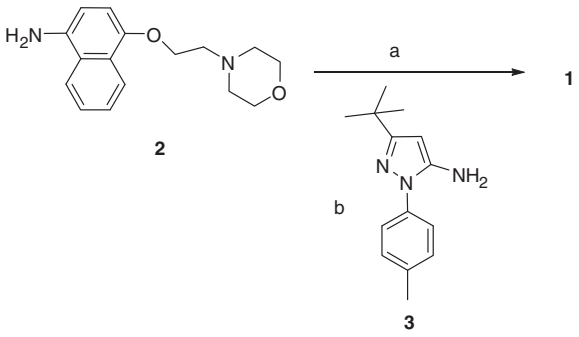
This process obviated the need to use phosgene on large scale and has been successfully implemented to produce hundreds of kilograms of BIRB796.



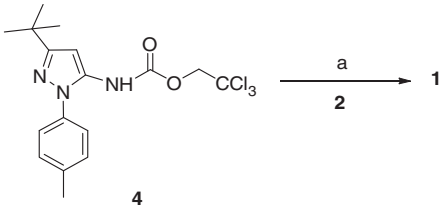
1

Figure 1. BIRB796.

Though highly practical and scalable, this method requires the preparation of amine **3**. Normally amine **3** is obtained by reacting *p*-tolylhydrazine with pivaloylacetonitrile. Since many arylhydrazines and ketonitriles are not commercially available and need to be synthesized, this approach makes it inconvenient and tedious



Scheme 1. Reagents and conditions: (a) dichloromethane, sodium bicarbonate, phosgene. 0 °C 15 min. (b) Compound **3**, *N*,*N*-diisopropylethylamine, THF, rt overnight.



Scheme 2. Reagents and conditions: (a) compound **2**, *N*,*N*-diisopropylethylamine, DMSO, 55–60 °C, 1.5 h.

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to prepare a series of analogs of BIRB796 that vary only at the N(1)-position of the pyrazole (Fig. 2). A more flexible synthesis was required by our Drug Discovery program for SAR studies and metabolite synthesis.

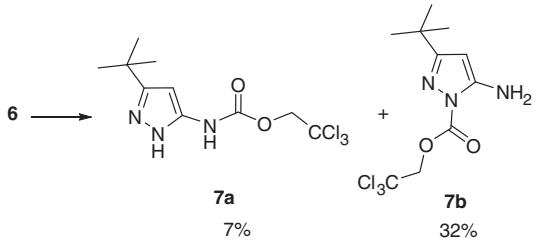
From retrosynthetic analysis of **1**, we envisioned that it might be possible to prepare **1** by the selective N-arylation of urea **5**, which should be readily accessible from the commercially available 3-(*tert*-butyl)-1*H*-pyrazol-5-amine **6**[6] and naphthalene amine **2**[7] through the carbamate process (Scheme 3).

We now wish to report a new synthesis of BIRB796 and its derivatives via the copper-mediated N-arylation of urea **5** with arylboronic acids which is suitable for drug discovery SAR studies and metabolite synthesis.[8]

2. Results and discussions

On the basis of our experience with urea formation, we began our study on urea **5** by treating 3-(*tert*-butyl)-1*H*-pyrazol-5-amine **6** with 2,2,2-trichloroethyl chloroformate in the presence of *N*, *N*-diisopropylethylamine in THF. Even at −10 °C, two major products (**7a** and **7b**) were obtained from this reaction and the selectivity of the reaction favored the undesired by-product **7b** (Scheme 4).[9]

Although the desired product could be isolated by chromatography, this approach suffered from a low yield early in the synthesis. On the other hand, when 4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-ylamine **2** was treated with 2,2,2-trichloroethyl chloroformate under the same conditions, the desired trichloroethyl carbamate **7c** was formed as the major product and was isolated



Scheme 4. Reagents and conditions: THF, *N*,*N*-diisopropylethylamine, 2,2,2-trichloroethyl chloroformate (0.9 equiv). −10 °C, 10 min.

in 88% yield after simple workup. The subsequent reaction between carbamate **7c** and amine **6** afforded urea **5** in 84% yield as the single product without the need for chromatographic purification (Scheme 5).[10]

With this key urea intermediate in hand, we turned our attention to copper-mediated arylation reactions.[11] Lam and Chan first reported that N–H and O–H containing compounds can be arylated at room temperature with arylboronic acids in the presence of cupric acetate.[12] Specifically, pyrazole was found to react with different arylboronic acids to give N-arylated products in good to moderate yields (Scheme 6).

Buchwald also reported a very general CuI-catalyzed N-arylation of amide and nitrogen heterocycles with aryl halides.[13a] Most recently, Sreedhar reported N-arylation of pyrazole in high yield with arylboronic acids using catalytic copper(I) oxide at room temperature without a base.[13b]

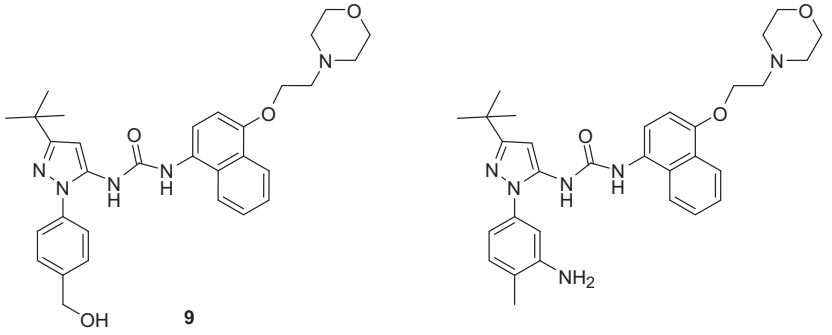
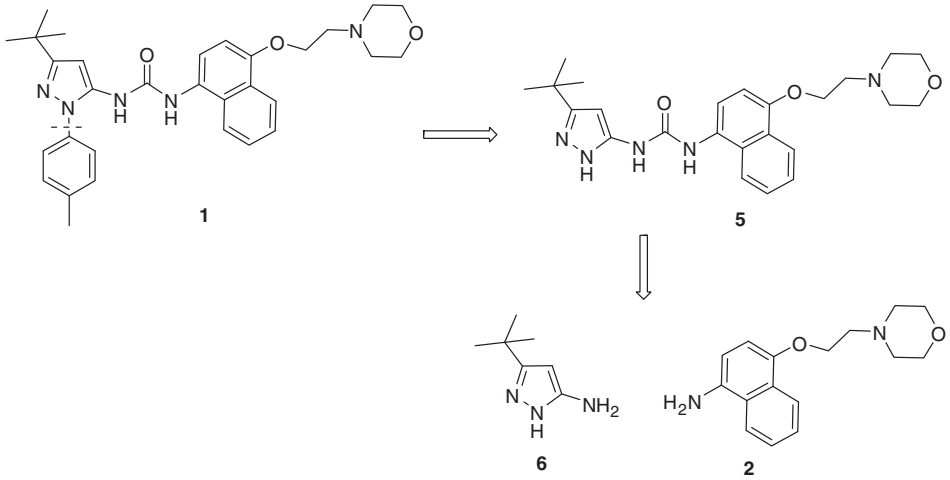
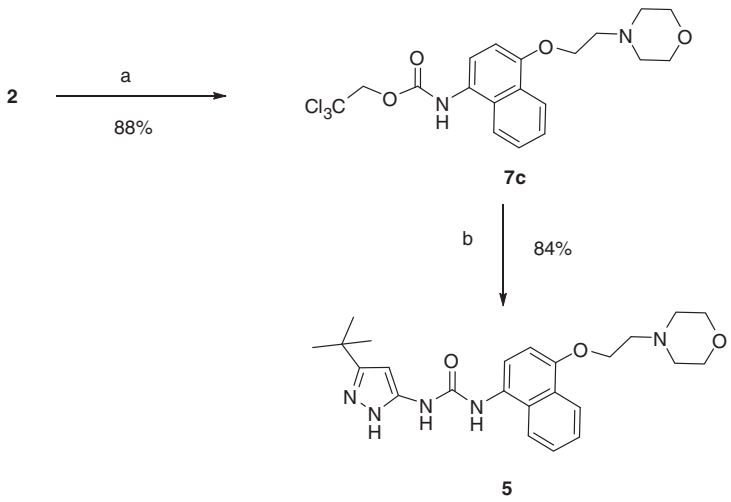


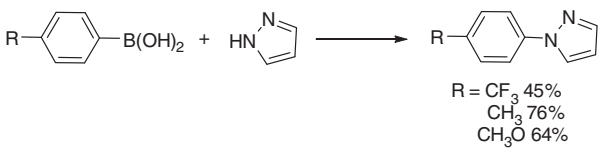
Figure 2. Pyrazole N(1)-substituted BIRB796 derivatives.



Scheme 3. Retrosynthetic analysis of BIRB796.



Scheme 5. Reagents and conditions: (a) 2,2,2-trichloroethyl chloroformate, *N*,*N*-diisopropylethylamine, THF, −10 °C, 40 min. (b) Compound **6**, *N*,*N*-diisopropylethylamine, DMSO, 80 °C, 14 h.



Scheme 6. Reagents and conditions: $Cu(OAc)_2$, pyridine, dichloromethane, MS, rt, 2 days.

One major concern for arylation of urea **5** was that the two urea N–H's might also react with the boronic acid under the same conditions to give two potential by-products (Fig. 3).

Using urea **5** as a substrate, we explored all the three previously mentioned N-arylation methods. Multiple products were obtained with CuI-catalyzed method, probably resulting from N-arylation on the urea N–H's of the compound. In our hand, even with stoichiometric amount of copper(I) oxide, urea **5** and *p*-tolylboronic acid failed to give any detectable BIRB796.

By subjecting urea **5** and *p*-tolylboronic acid to the copper acetate conditions, we were pleased to find that BIRB796 was formed as the major product and was isolated in 91% yield from the reaction after column chromatography (Scheme 7). Gratifyingly, no urea N-arylation product was detected by LC/MS. The major by-product was 4,4′-dimethylbiphenyl formed by homo-coupling of the *p*-tolylboronic acid. A small amount of the unreacted urea **5** was also recovered.[14]

Encouraged by this result, we then applied these conditions to a variety of commercially available arylboronic acids to explore the scope of this reaction in making *N*-aryl analogs of BIRB796. The results are listed in Table 1.[15]

As can be seen from Table 1, this arylating reaction tolerates a variety of functional groups. Simple arylboronic acids such as 4-tolyl, 4-*tert*-butyl, and biphenyl boronic acids gave 91%, 69%, and 70%

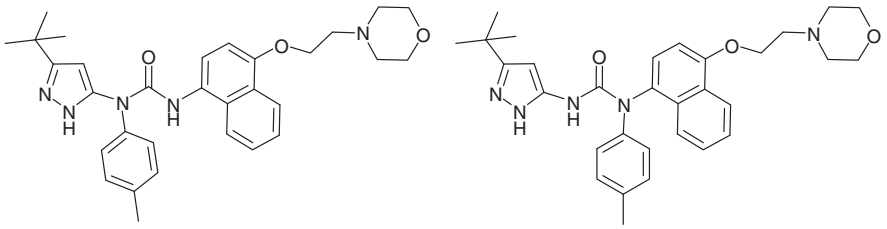
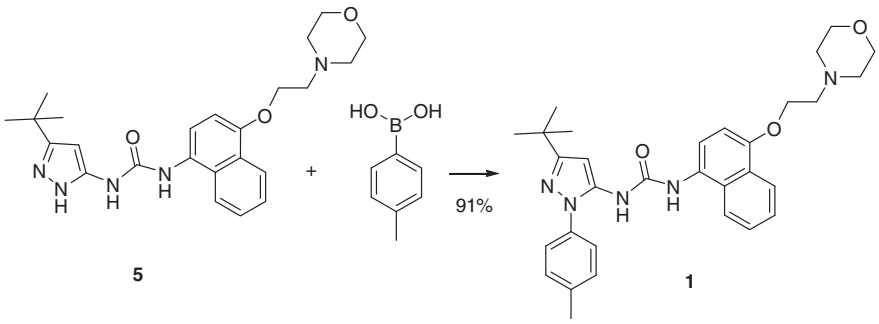
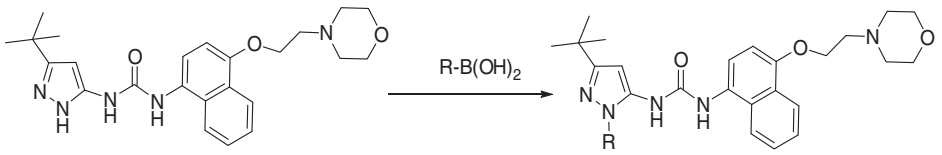


Figure 3. Two potential by-products.

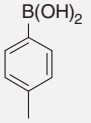
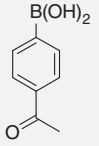
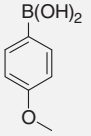
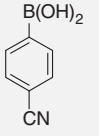
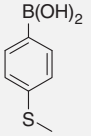
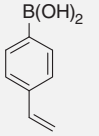
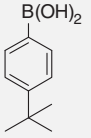
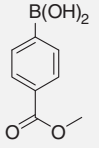
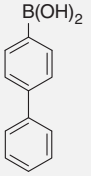
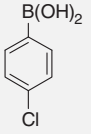
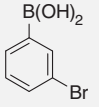


Scheme 7. Reagents and conditions: $Cu(OAc)_2$, pyridine, dichloromethane, MS, rt, 17 h.

Table 1

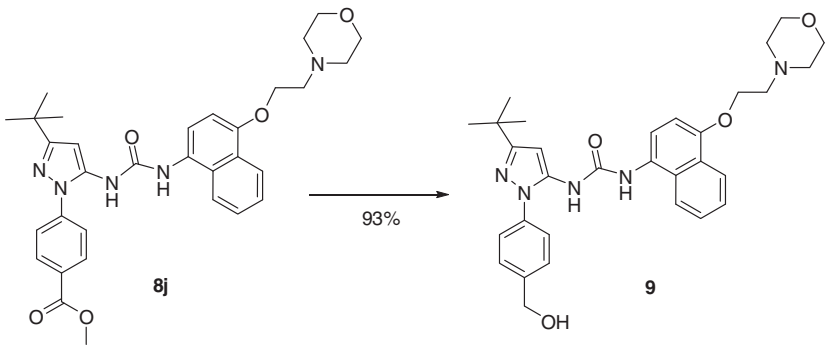


5 8

Entry	R-B(OH)$_2$	Product	Yield[a] (%)	Entry	R-B(OH)$_2$	Product	Yield[a] (%)
1		**1**	91	7		**8g**	55
2		**8a**	76	8		**8h**	49
3		**8b**	66	9		**8i**	66
4		**8d**	69	10		**8j**	71
5		**8e**	70	11		**8k**	25
6		**8f**	64	12		**8l**	51

[a] Isolated yield. Reaction conditions are not optimized.

yields, respectively (entries 1, 4, and 5). Cyanophenyl, acetylphenyl, and chlorophenyl boronic acids all worked well and gave the desired products (entries 6–8). Vinylphenyl boronic acid was also successfully utilized for this reaction (entry 9). Both *ortho*- and *meta*-substituted arylboronic acids were suitable substrates, though *ortho*-substituted arylboronic acids gave lower yields (entries 11 and 12). A slight electronic effect was observed, as more electron-deficient boronic acids gave reduced yields (entries 7 and 8). It is worth noting that 4-methoxycarbonylphenyl- boronic acid worked well to give compound **8j** in 71% yield (entry 10). This compound proved to be a very useful intermediate that can be readily reduced with $NaBH_4$/MeOH to give compound **9**, which is



8j 9

Scheme 8. Reagents and conditions: $NaBH_4$, methanol, rt, 1 h.

an important human metabolite of BIRB796 (Scheme 8).[16] The previous synthesis of **9** required a multi-step synthesis starting from 4-hydrazinobenzoic acid ethyl ester.[17]

In conclusion, we have described a new method for the expedient and facile access to BIRB796 and its N-arylated analogs in good to moderate yields. Direct cross-coupling of arylboronic acids with urea **5** in the presence of cupric acetate and base gave the corresponding products in one step. Key intermediate **5** was readily prepared from commercially available materials in good yield. This method uses inexpensive reagents and readily available starting materials under mild conditions. We believe that this new method should prove to be a useful alternative for the synthesis of BIRB796 and its derivatives.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.109.

References and notes

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6. 3-(*tert*-Butyl)-1*H*-pyrazol-5-amine **6** is commercially available in multi-kilogram quantities from several vendors.
7. Amine **2** is commercially available in gram quantities and can be prepared by following the procedures from Refs. 1 or 5.
8. Part of this work has been described in a patent, see: Tan, Z.; Song, J. J. PCT Int. Appl., WO 2002066442, 2002.
9. Structures of **7a** and **7b** were established by ^{1}H NMR and LC/MS. See Supplementary data for details.
10. *1-(3-tert-Butyl-1H-pyrazol-5-yl)-3-(4-(2-morpholino ethoxy)naphthalen-1-yl) urea* (**5**). A solution of 2,2,2-trichloroethyl 4-(2-morpholinoethoxy)naphthalen-1-yl carbamate (**7c**) (4.5 g, 10 mmol), 5-*tert*-Butyl-2-aminopyrazole (1.4 g, 10 mmol), and *N,N′*-diisoproplyethylamine (1.8 mL, 10 mmol) in DMSO (100 mL) was heated at 80 °C for 14 h. The mixture was cooled to room temperature. Ethyl acetate (100 mL) and water (100 mL) were added. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum to give the crude product. The crude product was triturated with ether, filtered, washed with hexane, and dried to give 3.7 g urea (**5**) as a beige solid. Yield (84%). Mp 206–207 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.08 (br s, 1H), 9.70 (br s, 1H), 9.21 (br s, 1H), 8.22 (d, J = 8.30 Hz, 1H), 8.09 (d, J = 8.40 Hz, 1H), 7.86 (d, J = 8.15 Hz, 1H), 7.61 (t, J = 7.35 Hz, 1H), 7.57 (t, J = 7.65 Hz, 1H), 6.98 (d, J = 8.45 Hz, 1H), 5.90 (br s, 1H), 4.26 (t, J = 5.55 Hz, 2H), 3.60 (t, J = 4.50 Hz, 4H), 2.85 (t, J = 5.55 Hz, 2H), 2.55 (br s, 4H), 1.28 (s, 9H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 153.0, 152.9, 150.3, 148.2, 127.5, 127.2, 126.5, 125.3, 125.3, 122.1, 121.4, 118.8, 105.2, 90.2, 66.2, 57.0, 53.6, 30.6, 29.9. MS(ES) m/z = 438 [M+H]$^{+}$.
11. For a recent review on copper-mediated C–O, C–N, C–S bond formation chemistry, see: Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. and references cited therein.
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14. The reaction solution was analyzed by LC/MS. Among the few by-products formed, none had a mass matching those of urea N-arylation isomers.
15. *General N-arylation procedure*. A mixture of 1-(3-*tert*-butyl-1H-pyrazol-5-yl)-3-(4-(2-morpholinoethoxy) naphthalen-1-yl) urea (**5**) (200 mg, 0.457 mmol), arylboronic acid (0.914 mmol, 2.0 equiv), copper(II) acetate (125 mg, 0.686 mmol, 1.5 equiv), pyridine (0.07 mL, 0.914 mmol, 2.0 equiv), and molecular sieves (300 mg, 4 Å, activated) in dichloromethane (10 mL) was stirred in a dry flask open to air at 21 °C for 17 h. The crude product mixture was purified by silica gel chromatography (0–10% ethanol/ethyl acetate) to give the product in the yields reported in Table 1. Copies of ^{1}H and ^{13}C NMR spectra of isolated products are provided as Supplementary data to demonstrate the homogeneity of samples. *1-(3-tert-Butyl-1-(4-methylphenyl)-1H-pyrazol-5-yl)-3-(4-(2-morpholinoethoxy)naphthalen -1-yl) urea* (**1**): mp 144–146 °C ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.79 (s, 1H), 8.59 (s, 1H), 8.21 (d, J = 7.95 Hz, 1H), 7.93 (d, J = 8.30 Hz, 1H), 7.66 (d, J = 8.35 Hz, 1H), 7.59–7.53 (m, 2H), 7.46 (d, J = 8.25 Hz, 2H), 7.37 (d, J = 8.20 Hz, 2H), 6.97 (d, J = 8.45 Hz, 1H), 6.39 (s, 1H), 4.26 (t, J = 5.55 Hz, 2H), 3.60 (t, J = 4.55 Hz, 4H), 2.85 (t, J = 5.55 Hz, 2H), 2.55–2.51 (m, 4H), 2.40 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.5, 152.6, 150.9, 137.5, 136.7, 136.2, 129.7, 128.4, 126.6, 126.3, 125.3, 125.2, 124.3, 122.0, 121.9, 120.5, 105.0, 94.9, 66.2, 57.0, 53.6, 32.0, 30.2, 20.6. MS(ES) m/z = 528 [M+H]$^{+}$.
16. 4-Hydroxymethylphenylboronic acid is commercially available. Unfortunately, no desired product was detected when it was used in the copper-mediated arylation reaction with urea **5**.
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