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Synthesis of unsymmetrical biaryl ureas from *N*-carbamoylimidazoles: kinetics and application

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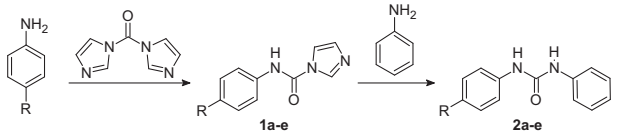
ABSTRACT

N-Carbamoylimidazoles dissociate in solution to yield imidazole and an isocyanate that may be reacted with another aryl amine to form an unsymmetrical biaryl urea. This paper investigates the reaction kinetics and the influence of electron withdrawing/donating substituents on the reaction of *N*-carbamoylimidazoles with aniline. The overall reaction mechanism involves two zwitterionic intermediates, formed during dissociation and upon reaction of the liberated isocyanate with aniline. The rate limiting step for the reaction is a base catalysed proton transfer from the second zwitterionic intermediate. Although electron withdrawing substituents on the aryl group hinder dissociation, they significantly increase reaction rates compared to compounds bearing electron donating substituents. The imidazole liberated upon dissociation catalyses the rate determining step so that reactions of dissociated *N*-carbamoylimidazoles proceed more rapidly than those involving only isocyanates. In addition, the imidazole eliminates the need for anhydrous reaction conditions. The *N*-carbamoylimidazole methodology was demonstrated by preparing sorafenib, a biaryl urea kinase inhibitor, in good yield and excellent purity.

1. Introduction

The biaryl urea motif is an important pharmacophore with numerous applications in pharmaceutical drugs and agrochemicals.[1,2] Unsymmetrical aryl urea compounds are generally prepared by the coupling of an aryl amine and aryl isocyanate. The limited availability of many isocyanates often necessitates their synthesis in the laboratory, commonly using phosgene or its equivalents. This methodology can be undesirable due to the toxicities of the isocyanates and phosgene, low yields resulting from the instabilities of the isocyanates, and the unwanted formation of symmetrical urea by-products. Due to the increasing importance of unsymmetrical biaryl urea compounds, considerable efforts have been directed towards the development of new, efficient and safe synthetic protocols. Numerous alternative methods have been reported.[1,3–5] However, their application is restricted by the use of expensive reagents and laborious reaction procedures, as well as formation of symmetrical urea by-products.

We examine here a straightforward synthetic procedure to prepare aryl urea compounds via *N*-carbamoylimidazole compounds (Scheme 1) and examine the influence of electron withdrawing/donating groups on the rates of the reactions. This facile procedure utilises *N*,*N*-carbonyldiimidazole (CDI), a common, inexpensive and easily handled crystalline solid.



Scheme 1. Synthesis of unsymmetrical biaryl ureas via *N*-carbamoylimidazoles.

Carbamoylimidazole compounds are readily prepared by treatment of an amine with CDI.[6,7] The carbamoylimidazole may then be used to prepare unsymmetrical ureas. The reaction of *N*,*N*-disubstituted carbamoylimidazoles with primary and secondary amines to prepare tri- and tetra-substituted ureas is well-known, and proceeds via a direct nucleophilic attack to the carbonyl group following activation with iodomethane.[6,8] The preparation of unsymmetrical ureas from *N*-carbamoylimidazole compounds has received significantly less attention. Rather than react via direct nucleophilic attack, it has been established that these compounds dissociate to an isocyanate and imidazole in solution, which may then react with amines to form unsymmetrical urea products.[9–11]

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Since this discovery almost 60 years ago, its synthetic application has been limited,[12–17] and no work has explored the kinetics of the reaction. However, as we show here, this reaction provides a useful pathway to prepare unsymmetrical aryl urea compounds.

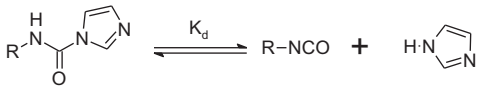
2. Results and discussion

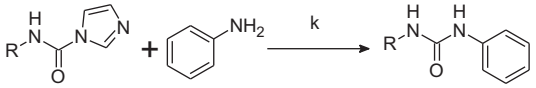
The *N*-carbamoylimidazole compounds, **1a**–**e** (Table 1), were prepared by the reaction of 4-substituted anilines with CDI at 50 °C for 18 h. **1a**–**e** precipitated from the reaction mixtures and were isolated as white solids, which showed no signs of degradation after three months at room temperature. For comparison, benzylcarbamoylimidazole, **1f**, was also prepared by a similar method.

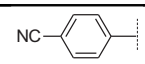
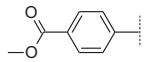
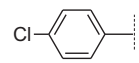
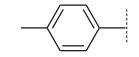
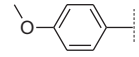
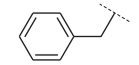
The ^{1}H NMR spectra of **1a**–**e** show variations attributed to the different electron withdrawing or donating strengths of the substituents. The electron withdrawing groups in **1a**–**c** cause a downfield shift in the aromatic proton resonances compared to those of the electron donating groups in **1d**–**e**. The chemical shifts of the N–H protons, which appear as broad low-field signals, are affected in a similar manner (Table 1). The influence of the substituents extends as far as the imidazole ring, with small shifts observed in the imidazole proton resonances across the series.

The ^{1}H NMR spectra of **1a**–**e** also contain additional sets of aromatic proton resonances. These are attributed to the aryl isocyanates that form upon dissociation of **1a**–**e** and are upfield from those of the un-dissociated compounds. Accompanying these signals are resonances at δ 7.51 and 6.95 from free imidazole. The dissociation constants (K_d) for the equilibria between **1a**–**e** and the corresponding aryl isocyanates and imidazole were determined from the ^{1}H NMR spectra and are shown in Table 1. Dissociation of the *N*-carbamoylimidazole compounds in solution proceeds via a two-step mechanism: diffusion-controlled transfer of the N–H proton to the imidazole group is followed by dissociation of the resulting zwitterionic intermediate to an isocyanate and imidazole (Fig. 1).[18] The ^{1}H NMR spectroscopic data of **1a**–**c** show that electron withdrawing substituents decrease the electron densities at the N–H protons (Table 1), and may therefore be expected to decrease the N–H pK_a values and increase the rate of proton transfer when forming the zwitterionic intermediate. However, consistent with previous findings,[11] electron withdrawing substituents decreased the amount of dissociation, while electron donating substituents increased the degree of dissociation. In contrast to **1a**–**e**, the benzyl substituted compound **1f** did not dissociate in solution. This was attributed to an absence of resonance stabilisation of the zwitterionic intermediate formed after the initial proton transfer step.

Table 1
^{1}H NMR spectroscopic data, dissociation constants (K_d) and rate constants for reactions of **1a**–**f** with aniline





	R	NH chemical shift (ppm)[a]	K_d[a,b]	Initial rate[c] (10^{-7} M s^{-1})	Yield of **2a**–**e** (%)[d]
1a		9.74	7.66×10^{-6}	3.46	84
1b		9.65	3.89×10^{-5}	0.963	63
1c		9.48	5.29×10^{-5}	0.507	77
1d		9.30	1.67×10^{-4}	0.0448	77
1e		9.24	3.01×10^{-4}	0.00205	63
1f		7.98	N/A	N/A	N/A

[a] ^{1}H NMR spectra recorded in THF-d_8. Concentrations of **1a**–**f** were 2 mM.
[b] Dissociations constants (K_d) for **1a**–**e**.
[c] Initial reaction rates for reactions of **1a**–**e** (10 mM) with aniline (10 mM) in THF at 20 °C.
[d] Isolated yields based on aniline for reactions in chloroform.

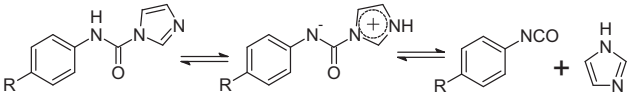


Fig. 1. Dissociation of an *N*-carbamoylimidazole via a zwitterionic intermediate.

Unsymmetrical ureas **2a**–**e** were prepared by reactions of **1a**–**e** with aniline. The reactions proceeded rapidly (<30 min) and in good yields (Table 1). **1f**, which does not dissociate in solution, failed to react with aniline and demonstrates that alkyl carbamoylimidazoles are not suitable starting materials for the preparation of ureas by this method. Interestingly, it was found that reactions of **1a**–**e** yielded pure products under non-anhydrous reaction conditions. The initial rates of the reactions of **1a**–**e** with aniline in THF at 20 °C were determined (Table 1). The substituents on the aryl group have a dramatic effect. Faster rates were observed for compounds **1a**–**c**, which bear electron withdrawing groups, compared to **1d**–**e**, which bear electron donating groups.

A linear relationship was observed between log rate and the Hammett substituent constants for the aromatic substituents (Fig. 2). From the slope of the line of best fit a reaction constant, ρ, of 2.69 was determined. A positive ρ value is characteristic of reactions that proceed more rapidly as the electron withdrawing character of the aryl substituent increases, and has been reported for the reaction of aromatic isocyanates with alcohols.[19] In contrast, the dissociation step, which is hindered by electron withdrawing groups, has a negative reaction constant (ρ=−1.51, Fig. 2). We hypothesised from this data that the rate determining step for this reaction occurs after liberation of the isocyanate.

That the dissociation of the *N*-carbamoylimidazoles is not rate determining was supported by the reaction orders determined for

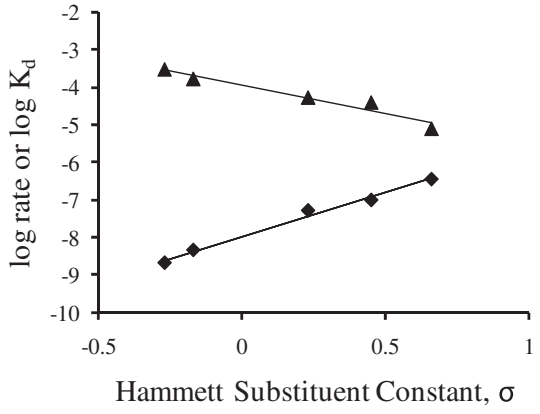


Fig. 2. Graph showing log rate (◆) and log K_d (▲) versus Hammett substituent constant.

1a–**e** and aniline using the method of initial rates. In all cases the reactions were found to be first order with respect to both **1a**–**e** and aniline; the appearance of aniline in the rate law excludes the possibility that dissociation of **1a**–**e** is rate limiting.

The role of the imidazole formed upon dissociation was investigated by comparing the initial reaction rate of **1d** with that of *p*-tolyl isocyanate (which is a dissociation product of **1d**. We measured the initial rates of reactions of these species with aniline in the solvents THF and acetonitrile (ACN) (Table 2). In both solvents, reactions of **1d** were faster than those of *p*-tolyl isocyanate despite the maximum concentration of *p*-tolyl isocyanate liberated from **1d** being ~0.5 mM (calculated from K_d). The enhanced rates of **1d** arise from base catalysed proton transfer from the zwitterion formed upon reaction of the isocyanate and aniline (Fig. 3).[20] That is, upon dissociation of **1d**, the free imidazole catalyses the proton transfer step (step 2 in Fig. 3). This was confirmed experimentally by including imidazole (0.58 mM for the dissociation of **1d**) in the reaction of aniline with *p*-tolyl isocyanate (Table 2, entry 5). The addition of imidazole accelerated the reaction, yielding a similar rate to that for **1d** under the same conditions (Table 2, entry 3). Even though aniline can act as both a reagent and proton transfer catalyst,[21] the increase in reaction rate upon addition of imidazole is a function of its greater basicity compared to aniline.

An important aspect of the reactions of **1a**–**e** with aniline is that undesired symmetrical biaryl ureas were not detected at any stage. Reactions involving isocyanates under non-anhydrous conditions can give rise to symmetrical ureas when amines, formed by isocyanate hydrolysis, react with another isocyanate. We therefore propose that the imidazole-catalyzed reactions are sufficiently rapid such that any water commonly found in AR grade solvents under ambient conditions does not hydrolyse the isocyanate intermediates, and obviates the need for strictly anhydrous conditions. This highlights the utility of the method to form exclusively unsymmetrical aryl urea compounds.

Table 2
Initial rates of reactions of **1d** and *p*-tolyl isocyanate with aniline at 20 °C

Entry	Reactant[a]	Conditions	Initial rate (10^{-9} M s^{-1})
1	**1d**	THF	2.04±0.01
2	*p*-Tolyl isocyanate	THF	1.92±0.05
3	**1d**	ACN	1.90±0.02
4	*p*-Tolyl isocyanate	ACN	1.48±0.08
5	*p*-Tolyl isocyanate	ACN+imidazole[b]	2.01±0.03

[a] [Compound **1d**]$_{t=0}$=[*p*-tolyl isocyanate]=2.00 mM. [Aniline]=5.00 mM.
[b] The imidazole concentration was 0.58 mM, which was calculated using the K_d value determined for **1d**.

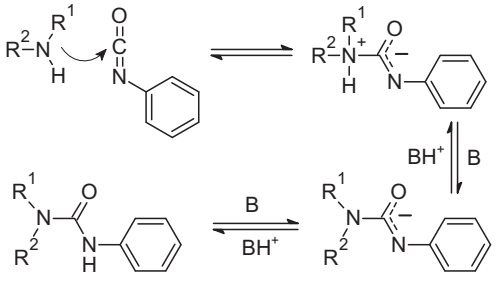
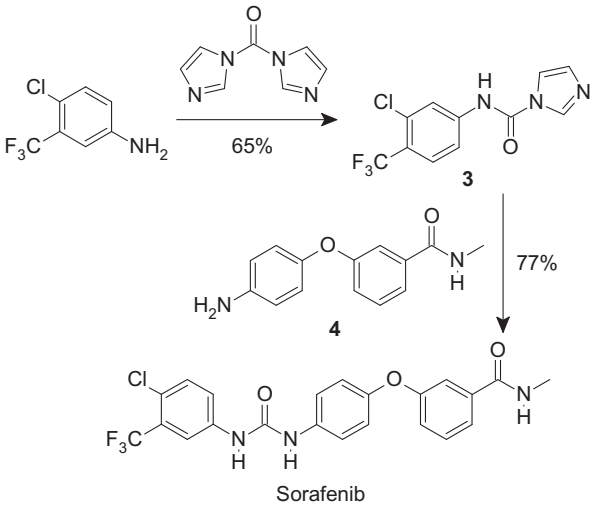


Fig. 3. Reaction mechanism for the base catalysed reaction of isocyanates with weakly basic amines.[20]

We applied the *N*-carbamoylimidazole methodology to the synthesis of sorafenib (Scheme 2), in a two-step adaptation of a literature[22] procedure. Sorafenib is a novel biaryl urea multi-targeted kinase inhibitor marketed as Nexavar® by Bayer for the treatment of advanced renal cell and hepatocellular carcinomas. By virtue of its low toxicity, broad spectrum anticancer activity and novel multi-targeted mechanism of action, sorafenib is the subject of ongoing optimization studies.[17,23–27] A key step in the synthesis of sorafenib is construction of the unsymmetical urea moiety, which is generally achieved by reaction of amine **4** (shown in Scheme 2) with 4-chloro-3-(trifluoromethyl)-phenyl isocyanate.[22,28] The procedure suffers the problems associated with use of isocyanates, and the product may require HPLC purification.[28] Furthermore, due to the limited range of commercially available aryl isocyanates, preparation of structurally diverse analogues requires isocyanate synthesis using phosgene or equivalents. Recently, the use of phenyl carbamates was reported as a safe isocyanate alternative, however reaction yields were moderate (48–62%).[29] We found that the *N*-carbamoylimidazole methodology offered a facile, non-hazardous and high yielding route to sorafenib. Carbamoylimidazole **3**, readily prepared from CDI and 4-chloro-3-(trifluoromethyl)-aniline, reacted rapidly with **4**, affording sorafenib in high yield (77%). Pure product was obtained without the need for anhydrous conditions or chromatographic purification. The procedure is amenable to the synthesis of sorafenib analogues, which is likely to be of great future utility as the need for novel analogues for the treatment of drug-resistant clonal tumour populations increases.



Scheme 2. Synthesis of sorafenib via *N*-carbamoylimidazole **3**.

3. Conclusions

In conclusion, we have prepared several examples of unsymmetrical aryl urea compounds starting from *N*,*N*-carbonyldiimidazole and substituted aromatic amines. The reaction proceeds via the formation of two zwitterionic intermediates. The overall reaction rate is independent of the degree of dissociation and is enhanced by electron withdrawing substituents. Imidazole released during the dissociation of the *N*-carbamoylimidazoles catalyses the reaction of the liberated isocyanate and obviates the need for anhydrous reaction conditions. Overall, *N*-carbamoylimidazole compounds are useful synthetic reagents that permit rapid, safe and straightforward access to unsymmetrical ureas in good yield and purity.

4. Experimental

4.1. General

All chemicals and anhydrous solvents were purchased from Sigma Aldrich (Castle Hill, Australia). Biaryl ether **4** was synthesised according to a literature procedure.[22] ^{1}H NMR and ^{13}C NMR spectra

were recorded using a Varian 400-MR instrument operating at 400 MHz. Spectra were referenced internally to NMR solvent (THF-d_8; ^{1}H δ 1.73. DMSO-d_6; ^{1}H δ 2.48, ^{13}C δ 40.45). Because *N*-carbamoylimidazoles **1a**–**e** and **3** dissociate in solution their NMR spectra contain resonances arising from the parent compounds and their dissociation products. Resonances attributed to dissociated imidazole and isocyanate species are labelled with 'im' and 'iso', respectively. Melting points were measured on a Stuart SMP10 melting point apparatus. We note that *N*-carbamoylimidazoles **1a**–**e** displayed broad melting points, which were attributed to thermal decomposition of these compounds.[30] Elemental analyses were carried out by the Microanalytical Unit at the Research School of Chemistry, Australian National University.

4.2. Syntheses

*4.2.1. General procedure for the synthesis of **1a**–**f**.* CDI (1.055 g, 6.5 mmol) was suspended in anhydrous 1,2-dichloroethane (10 mL) under nitrogen. The substituted aniline (4.7 mmol) was added, and the mixture was heated to 50 °C, during which time a clear solution was obtained. After stirring for 18 h, the resulting suspension was cooled in an ice bath for 1 h. The solid was collected by filtration and washed with 1,2-dichloroethane, yielding **1a**–**f** as white solids.

*4.2.1.1. N-(4-Cyanophenyl)-1H-imidazole-1-carboxamide (**1a**).* Yield 0.751 g (75%); mp (decomp.)=165–187 °C. ^{1}H NMR (400 MHz, THF-d_8): δ 9.74 (s, 1H), 8.23 (s, 1H), 7.89–7.78 (m, 2H, AA′BB′), 7.77–7.70 (m, 2H, AA′BB′), 7.64 (d, J=0.8 Hz, 1H), 7.35–7.30 (m, 0.12H, AA′BB′, iso), 7.29–7.25 (m, 0.12H, AA′BB′, iso), 7.03 (d, J=0.8 Hz, 1H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 152.2, 137.1, 135.6 (im), 133.9, 133.8 (iso), 130.2, 124.7 (iso), 121.2 (im), 119.6, 118.7, 113.9. ESI-MS: m/z (%): 213 ([M+H]$^+$). Anal. Calcd for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 61.95; H, 3.71; N 26.43.

*4.2.1.2. Methyl 4-[(1H-imidazol-1-ylcarbonyl)amino]benzoate (**1b**).* Yield 0.961 g (83%); mp (decomp.)=166–180 °C. ^{1}H NMR (400 MHz, THF-d_8): δ 9.65 (s, 1H), 8.23 (s, 1H), 8.08–7.90 (m, 2H, AA′BB′), 7.80–7.70 (m, 2H, AA′BB′), 7.65 (d, J=1.6 Hz, 1H), 7.51 (s, 0.13H, im), 7.28–7.22 (m, 0.26H, AA′BB′, iso), 7.03 (d, J=1.6 Hz, 1H), 6.95 (s, 0.26H, im), 3.85 (s, 3H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 166.2, 152.3, 137.0, 135.6 (im), 131.5 (iso), 130.8, 130.7, 130.2, 125.5 (iso), 120.5 (im), 120.6, 118.0, 117.6. ESI-MS: m/z (%): 246 ([M+H]$^+$). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.66; H, 4.52; N 17.03.

*4.2.1.3. N-(4-Chlorophenyl)-1H-imidazole-1-carboxamide (**1c**).* Yield 0.721 g (69%); mp (decomp.)=151–188 °C. ^{1}H NMR (400 MHz, THF-d_8): δ 9.48 (s, 1H), 8.20 (s, 1H), 7.66–7.56 (m, 3H), 7.52–7.46 (m, 0.45H), 7.38–7.30 (m, 2H, AA′BB′), 7.24–7.20 (m, 0.30H, AA′BB′, iso), 7.01 (d, J=1.6 Hz, 1H), 6.95 (s, 0.30H, im). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 152.8, 138.9, 135.6 (im), 130.1 (iso), 129.2, 129.1, 128.9, 128.7, 125.9 (iso), 122.9, 120.3 (im), 117.5. ESI-MS: m/z (%): 224 ([M+H]$^+$). Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.44; H, 3.74; N 19.12.

*4.2.1.4. N-(4-Methylphenyl)-1H-imidazole-1-carboxamide (**1d**).* Yield 0.693 g (73%); mp (decomp.)=136–148 °C. ^{1}H NMR (400 MHz, THF-d_8): δ 9.30 (s, 1H), 8.19 (d, J=0.8 Hz, 1H), 7.65 (s, 0.25H), 7.61 (d, J=0.8 Hz, 1H), 7.55–7.45 (m, 2H, AA′BB′), 7.38–7.32 (m, 0.50H, AA′BB′, iso), 7.20–7.10 (m, 2H, AA′BB′), 7.05–6.95 (m, 1.50H), 6.94 (s, 0.50H, im), 2.31 (s, 3H), 2.29 (s, 0.75H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 153.1, 137.7, 135.6 (im), 130.9, 130.6, 129.7 (iso), 129.6, 125.6 (iso), 121.6 (im), 118.6, 117.5. ESI-MS: m/z (%): 202 ([M+H]$^+$). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.52; H, 5.52; N 20.82.

*4.2.1.5. N-(4-Methoxyphenyl)-1H-imidazole-1-carboxamide (**1e**).* Yield 0.514 g (50%); mp (decomp.)=116–152 °C. ^{1}H NMR (400 MHz, THF-d_8): δ 9.24 (s, 1H), 8.18 (d, J=0.8 Hz, 1H), 7.60 (d, J=0.8 Hz, 1H), 7.56 (s, 0.36H), 7.55–7.45 (m, 2H, AA′BB′), 7.40–7.53 (m, 0.72H, AA′BB′, iso), 6.99 (d, J=0.8 Hz, 1H), 6.94 (s, 0.72H, im), 6.90–6.80 (m, 2H, AA′BB′), 6.80–6.75 (m, 0.72H, AA′BB′, iso), 3.77 (s, 3H), 3.72 (s, 1.08H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 156.7, 154.7, 153.4, 136.7, 135.6 (im), 130.1, 133.4, 130.6, 130.1 (iso), 123.4 (iso), 120.3 (im), 117.4, 114.5, 114.4, 55.7, 55.6. ESI-MS: m/z (%): 218 ([M+H]$^+$). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.90; H, 5.36; N 19.63.

*4.2.1.6. N-(Benzyl)-1H-imidazole-1-carboxamide (**1f**).* Yield 0.807 g (85%); mp=124–125 °C. ^{1}H NMR (400 MHz, THF-d_8): δ 8.08 (s, 1H), 7.98 (s, 1H), 7.49 (d, J=1.2 Hz, 1H), 7.40–7.20 (m, 5H), 6.94 (d, J=1.2 Hz, 1H), 4.53 (d, J=1.6 Hz, 2H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 149.4, 138.9, 136.5, 130.1, 128.9, 128.6, 127.7, 127.6, 127.4, 117.1, 43.9. ESI-MS: m/z (%): 202 ([M+H]$^+$). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.46; H, 5.23; N 20.93.

*4.2.2. General procedure for the synthesis of **2a**–**e**.* Compound **1a**–**e** (1.28 mmol) were dissolved in the minimum volume of chloroform at 50 °C, and aniline (0.060 g, 0.65 mmol) was added. The solution was stirred for 30 min at 50 °C and then cooled in an ice bath for 10 min. The resulting solids were collected by filtration and washed with cool chloroform, yielding the biaryl ureas **2a**–**e** as white solids.

*4.2.2.1. 1-(4-Cyanophenyl)-3-phenylurea (**2a**).* Yield 0.129 g (84%); mp=205–206 °C. ^{1}H and ^{13}C NMR data are in good agreement with previously reported data.[3]

*4.2.2.2. Methyl 4-[(phenylcarbamoyl)amino]benzoate (**2b**).* Yield 0.110 g (63%); mp=176–178 °C (lit. mp=178 °C).[31] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.84 (s, 1H), 7.87 (AA′BB′, 2H), 7.57 (AA′BB′, 2H), 7.44 (dd, J=8.4, 1.2 Hz, 2H), 7.29 (t, J=7.6 Hz, 2H), 6.99 (tt, J=7.6, 1.2 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 166.6, 152.7, 144.8, 139.7, 130.9 (2C), 129.3 (2C), 122.9, 122.8, 118.9 (2C), 117.8 (2C), 52.3.

*4.2.2.3. 1-(4-Chlorophenyl)-3-phenylurea (**2c**).* Yield 0.122 g (77%); mp=247–250 °C (lit. mp=250–253 °C).[32] ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.79 (s, 1H), 8.68 (s, 1H), 7.47–7.41 (m, 4H), 7.31–7.24 (m, 4H), 6.95 (t, J=7.6 Hz, 1H). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 152.9, 139.9, 139.1, 129.3 (2C), 129.1 (2C), 125.8, 122.5, 120.2 (2C), 118.8 (2C).

*4.2.2.4. 1-(4-Methylphenyl)-3-phenylurea (**2d**).* Yield 0.112 g (77%); mp=212–213 °C (lit. mp=212–213 °C).[33] ^{1}H and ^{13}C NMR data are in good agreement with previously reported data.[3]

*4.2.2.5. 1-(4-Methoxyphenyl)-3-phenylurea (**2e**).* Yield 0.097 g (63%); mp=193–194 °C (lit. mp=198 °C).[4] ^{1}H and ^{13}C NMR data are in good agreement with previously reported data.[3]

*4.2.3. N-[4-Chloro-3-(trifluoromethyl)phenyl]-1H-imidazole-1-carboxamide (**3**).* To a solution of 4-chloro-3-(trifluoromethyl)aniline (2.000 g, 10.23 mmol) in anhydrous 1,2-dichloroethane (15 mL) under nitrogen, was added CDI (2.321 g, 14.32 mmol). The solution was stirred at 45 °C for 16 h, and then at room temperature for 3 h. The solid was collected by filtration and washed with 1,2-dichloroethane, affording 1.925 g (65%) of **3** as a white solid. Mp=115–118 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=8.39 (t, J=1.2 Hz, 1H), 8.13 (d, J=2.8 Hz, 1H), 7.94 (dd, J=8.8, 2.8 Hz, 1H), 7.80 (t, J=1.2 Hz, 1H), 7.74 (d, J=8.8 Hz, 1H), 7.62 (d, J=0.8 Hz, 0.7H, im), 7.23 (d, J=8.8 Hz, 0.7H, iso), 7.09 (m, 1H), 6.99 (m, 1.4H, im), 6.96 (d,

J=2.8 Hz, 0.7H, iso), 6.75 (dd, J=8.8, 2.8 Hz, 0.7H, iso). ^{13}C NMR (100.5 MHz, DMSO-d_6): δ 152.8, 147.4, 139.4, 137.7, 136.9, 135.6 (im), 132.7 (iso), 130.3, 127.4, 127.3, 127.1, 127.0, 125.9, 125.8 (iso), 123.9, 123.3, 122.1, 121.9 (im), 120.0, 119.9, 119.8, 119.7, 117.5. MS (ESI): m/z=290 $[M+H]^+$.

4.2.4. 4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-phenoxy]-N-methylpyridine-2-carboxamide (sorafenib). To a solution of **3** (1.873 g, 6.47 mmol) in ethyl acetate (20 mL) at 50 °C, was added **4** (0.983 g, 4.04 mmol). The solution was stirred for 45 min, and then at room temperature for 2 h. The precipitate was collected by filtration, washed with cold ethyl acetate, and dried in vacuo, affording 1.443 g (77%) of sorafenib as a white solid. ^{13}C NMR (100.5 MHz, DMSO-d_6): δ=166.4, 164.3, 152.9, 152.8, 150.8, 148.3, 139.8, 137.5, 132.5, 127.0 (q, J_{C-F}=122 Hz, 1C), 124.6, 123.6, 122.8, 121.9, 121.0, 117.3, 117.2, 117.2, 114.5, 109.1, 26.5. The ^{1}H NMR spectrum of the product is in good agreement with previously reported data.[22] MS (ESI): m/z=466 $[M+H]^+$. $C_{21}H_{16}N_4O_3ClF_3$ (464.82): calcd. C 54.26, H 3.47, N 12.05; found C 54.18, H 3.38, N 11.99.

4.3. Determination of dissociation constants (k_d)

Solutions of **1a**–**f** in THF-d_8 were accurately prepared (2.00 mM). ^{1}H NMR spectra of the solutions were recorded at 5 min intervals with the temperature set to 20 °C, until equilibrium was established. The low-field aromatic resonances assigned to the undissociated compounds, and the upfield aromatic resonances assigned to the isocyanates were selected as diagnostic. The averaged integration areas of these resonances were used to reflect the concentrations of **1a**–**f** and the dissociated isocyanate. Dissociation constants were calculated from the concentrations of these species at equilibrium.

4.4. Initial rate experiments

Stock solutions of 5.00 mM **1a**–**e** and 50.00 mM aniline in anhydrous THF were combined in sealed reaction vessels with additional anhydrous THF to give three solutions with the following concentrations: (1) [**1a**–**e**]=1.00 mM, [aniline]=5.00 mM; (2) [**1a**–**e**]=1.00 mM, [aniline]=10.00 mM; (3) [**1a**–**e**]=2.00 mM, [aniline]=10.00 mM. The solutions were magnetically stirred at 20 °C with the temperature maintained by means of a thermostated water bath. 0.5 mL samples of the reactions were taken at set time points (typically every 5 min for rapid reactions, and every 40 min for slower reactions), and quenched with *tert*-butyl amine (100 μL, >100 fold excess relative to aniline) in acetonitrile (9.5 mL). The reaction aliquots were then analyzed for the formation of the urea product by LC/MS. Four time points were collected for each reaction. In all cases plots of urea formation versus time were linear (R^2>0.98), and the slopes of the lines were used to determine the initial rate of the reactions. Plots of log rate versus log [**1a**–**e**] for experiments (1) and (2), and (2) and (3) were used to determine the reaction orders for **1a**–**e** and aniline.

4.5. Initial rate comparison experiments

Stock solutions of 5.00 mM **1d**, 5.00 mM *p*-tolyl isocyanate, 5.00 mM imidazole and 50.00 mM aniline were prepared in anhydrous THF and acetonitrile, and combined in sealed reaction vessels to give solutions of the following concentrations: (1) [**1a**–**e**]=2.00 mM, [aniline]=5.00 mM in THF and acetonitrile; (2) [*p*-tolyl isocyanate]=2.00 mM, [aniline]=5.00 mM in THF and acetonitrile; (3) [*p*-tolyl isocyanate]=2.00 mM, [aniline]=5.00 mM, [imidazole]=0.58 mM in acetonitrile. Reactions were maintained at 20 °C by means of a thermostated water bath. Reaction sampling was performed as described above. Samples were taken at 0, 15, 30 and 45 min. Plots of reaction progress versus time were linear (R^2<0.99).

4.6. LC/MS analyses

Reaction aliquot analyses were performed on a Thermo Scientific TSQ Quantum Access Max LC/MS/MS system (San Jose CA, USA) fitted with a Thermo Hypersil GOLD column (2.1 mm×150 mm, 5 μm particle size, San Jose CA, USA). The mobile phase was 55% acetonitrile in water containing 0.1% formic acid, and the flow rate was 0.30 mL/min. Automated injections (20 μL) were used, and samples were stored at 5 °C in the autosampler. The LC/MS interface used electrospray ionization operating in the positive ionization mode with high purity nitrogen (BOC, Sydney, NSW, Australia) as the sheath gas at 35 psi. Selected ion monitoring was used. In all cases baseline separation between the diaryl reaction product **2a**–**e** and other reaction species was achieved. Xcalibur 2.1 Software and Microsoft Excel 2007 were used in data acquisition and analysis.

Calibration curves were constructed from **2a**–**e** to quantify the formation of the biaryl reaction products. Stock solutions of **2a**–**e** were prepared from accurately weighed samples, and calibration solutions were prepared by serial dilution.

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