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CONVENIENT SYNTHESIS OF SORAFENIB AND ITS DERIVATIVES

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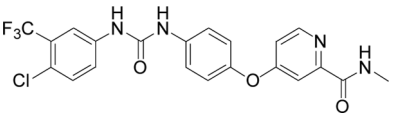
GRAPHICAL ABSTRACT



Abstract *This article describes a convenient synthesis of sorafinib and its derivatives from phenyl carbamates in good yields. This procedure, avoiding toxic phosgene, is especially suitable for large-scale preparation.*

Keywords Aminolysis; phenyl carbamate; sorafenib; unsymmetrical urea

INTRODUCTION

Hepatocelluar carcinoma (HCC) is a serious health problem that has been neglected until recently. During the past decades, the heavy burden of viral hepatitis C as well as the growing importance of nonalcoholic steatohepatitis have resulted in dramatic increases in HCC incidence in Western countries.[1] Sorafenib (compound **1a**) is an oral multikinase inhibitor that blocks tumor cell proliferation and angiogenesis by targeting the serine/threonine kinases Raf-1/B-Raf and the tyrosine kinases (RTKs) of VEGFR -2/-3 and PDGFR-β.[2] It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced renal cell carcinoma in 2005[3] and hepatocelluar carcinoma in 2007.[4] Nowadays, several reports have documented the preparation of sorafenib (Scheme 1). The key step is the construction of the unsymmetrical urea moiety. The classical method was the reaction of isocyanate **4** with the aniline **2**. Another reported method was the direct coupling of the amine **2** with aniline **3** in the presence of 1,1′-carbonyldiimidazole (CDI). Because the preparation of isocyanate **4** has to use very toxic phosgene, this process was not appealing for large-scale preparation. Besides, in our preparation of the sorafenib's

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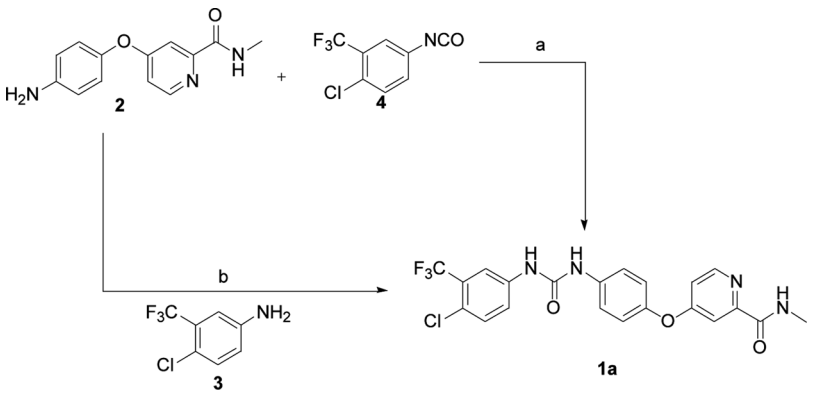


Scheme 1. Two reported methods for synthesis of sorafenib. Reagents and conditions: (a) CH_2Cl_2, 92% yield. (b) CH_2Cl_2, CDI, 91% yield.

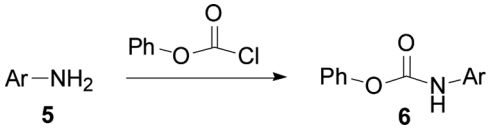
derivatives, the second CDI procedure found that the yield was poor and the reaction was rather complicated (Scheme 1).[5,6] Obviously, a harmless and convenient synthetic method for sorafenib and its derivatives is still needed. In this article, we describe an improved and practical synthetic method for sorafenib and its analogs.

RESULTS AND DISCUSSION

Sorafenib is a molecule possessing a structure of *N,N*-unsymmetrical substituted urea. *N,N*-Unsymmetrical substituted ureas have so many applications in medicinal chemistry that lots of methods have been reported for its preparation. Most of the methods are based on phosgene, phosgene substitutes, carbonic acid derivatives, and isocyanates.[7] However, these methods use highly toxic reagents such as phosgene.

Recently, some methods for the synthesis of unsymmetrical ureas without any toxic reagents have been also developed.[8] One promising method was the aminolysis of alkoxycarbonylated amines. Of the alkoxycarbonylated amines, Matsumura together with his coworkers proved that phenyl carbamate was the better choice.[9] Thus, it has inspired us to use this method to explore the synthesis of sorafenib and its derivatives.

First, one substrate aniline **2** was prepared from 4-chloro-pyridine-2-carboxylic acid methylamide via the substitution reaction.[6] Meanwhile, *o*-tolylamine was chosen to synthesize the other substrate phenyl carbamate **6b** by reacting with phenyl chloroformate (Scheme 2).[10,11] Then we found the reaction of the substrate aniline **2** with phenyl carbamate **6b** in the presence of base gave the desired unsymmetrical

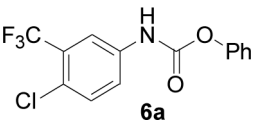
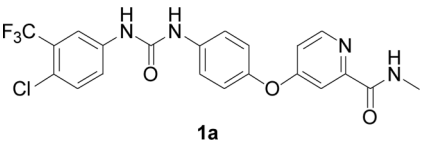
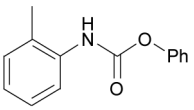
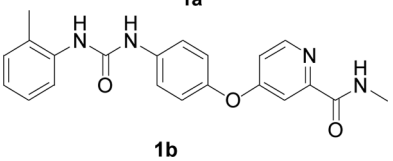
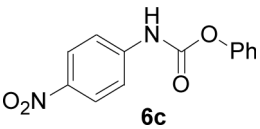
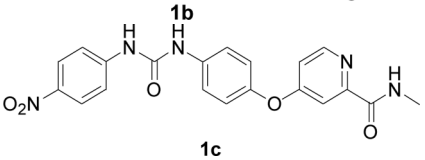
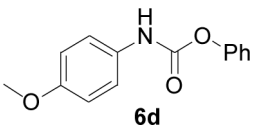
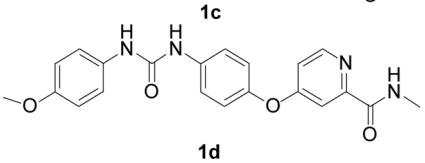
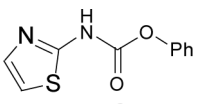
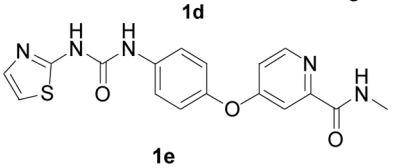


Scheme 2. Method for synthesis of phenyl carbamate.

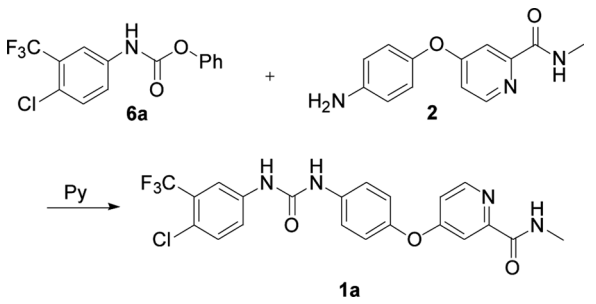
urea **1b** in 52.2% yield. Based on the fact, several anilines, which contained either electron-withdrawing group, electron-donating group, or heterocycle, were selected to synthesize different phenyl carbamates **6c–6e** by the same strategy (Scheme 2). These phenyl carbamates **6c–6e** were checked for whether they could react with the substrate amine **2**. As expected, all the synthesized phenyl carbamates **6b–6e** could react well with the substrate aniline **2** in good yields, as shown in Table 1. Therefore, it could be concluded that the electronegativity of the anilines **5**, which were used to prepare phenyl carbamates **6**, had little influence on the reactivity between the phenyl carbamates **6** and the substrate aniline **2**. Moreover, the method had a considerable degree of applicability in the synthesis of unsymmetrical ureas.

According to the synthesis of these unsymmetrical ureas, we developed a novel route to synthesize sorafenib. First, phenyl carbamate **6a** was obtained similar to compounds **6b–6e**. Subsequently, phenyl carbamate **6a** was treated with the aniline **2** and ammonolyzed in the presence of base (Scheme 3) to produce sorafenib in 48.2% yield. After chromatography, sorafenib was obtained in better than 99% purity. In the experiments, phenyl carbamate **6a** reacts with aniline **2** smoothly regardless of

Table 1. Preparation of sorafenib's derivatives

Carbonate[a]	Product	Yield[b]
 **6a**	 **1a**	48.2%
 **6b**	 **1b**	52.2%
 **6c**	 **1c**	54.8%
 **6d**	 **1d**	54%
 **6e**	 **1e**	62.5%

[a]Prepared by the reported methods.
[b]Yield after chromatography.



Scheme 3. Our approach for synthesis of sorafenib.

whether the solvent was pyridine or other basic organic solution. The effectiveness and robustness of this procedure were undiminished on a preparative scale.

In summary, a convenient and harmless method was developed for the synthesis of sorafenib and its derivatives. Our approach avoided the toxic reagents. The yield was good, and the route was suitable for large-scale preparation.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) instruments. ^{13}C NMR spectra were obtained on JNM-EX400 (400 MHz) and Bruker DRX-500 (500 MHz) instruments. All reagents were used directly as obtained commercially, unless otherwise noted.

General Procedure for Phenyl Carbamate 6

Phenyl chloroformate 1.5 g (9.5 mmol) was added to a solution of aniline **2** 1 g (8 mmol) and pyridine 0.77 ml (9.5 mmol) in dichloromethane at 0 °C, and then the mixture was stirred at room temperature for 1 h. After the reaction was completed, 10 ml water and 1 ml dilute hydrochloric acid was added, extracted with dichloromethane, dried over sodium sulfate, and evaporated under vacuum to produce the product.

(4-Chloro-3-trifluoromethyl-phenyl)-carbamic Acid Phenyl Ester 6a[12]

Yield 93.8%. ^{1}H NMR ($CDCl_3$): δ 7.11 (s, 1 H), 7.18 (d, $J = 8$ Hz, 2 H), 7.27 (m, 2 H), 7.41 (m, 2 H), 7.45, $J = 8$ Hz, 1 H), 7.60 (d, $J = 8$ Hz, 1 H), 7.81 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 120.88, 121.46, 122.72, 126.08, 126.34, 129.51, 129.57, 132.09, 136.35, 150.24, 151.61. Mp: 109–111 °C.

o-Tolyl-carbamic Acid Phenyl Ester 6b[13]

Yield 93%. ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 1 H), 6.73 (s, 1 H), 7.06 (m, 1 H), 7.22–7.29 (m, 5 H), 7.41 (m, 2 H), 7.86 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.58, 120.84, 121.54, 124.58, 125.55, 126.91, 129.32, 130.45, 135.35, 150.68. Mp: 94–95 °C.

(4-Nitro-phenyl)-carbamic Acid Phenyl Ester 6c[14]

Yield 85%. ^{1}H NMR ($CDCl_3$): δ 7.19 (d, $J = 8$ Hz, 2 H), 7.28 (m, 2 H), 7.42 (m, 2 H), 7.62 (d, $J = 9$ Hz, 2 H), 8.23 (d, $J = 9$ Hz, 2 H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 118.4, 120.95, 121.44, 125.25, 126.23, 129.59, 143.32, 143.39, 150.07, 151.11. Mp: 159–160 °C.

(4-Methoxy-phenyl)-carbamic Acid Phenyl Ester 6d[15]

Yield 81%. ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 3 H), 6.72 (s, 1 H), 6.88 (d, $J = 9$ Hz, 2 H), 7.18 (d, $J = 8$ Hz, 2 H), 7.24 (d, $J = 7$ Hz, 1 H), 7.35–7.40 (m, 4 H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 55.47, 114.29, 120.64, 121.64, 125.58, 129.35, 150.63. Mp: 154–155 °C.

Thiazol-2-yl-carbamic Acid Phenyl Ester 6e[16]

Yield 93%. ^{1}H NMR ($CDCl_3$): δ 6.97 (s, 1 H), 7.27 (m, 3 H), 7.43 (m, 2 H), 7.50 (d, $J = 4$ Hz, 1 H), 12.30 (s, 1 H). ^{13}C NMR (500 MHz, $CDCl_3$): δ113.20, 121.46, 126.14, 129.56, 137.03, 150.44, 152.49, 161.64. Mp: 182–184 °C.

General Procedure for Sorafenib and Its Derivatives

A 25-mL flask was charged with 5 mL pyridine, 200 mg amine **2** (0.822 mmol), and 259.5 mg phenyl carbamate **5** (0.822 mmol), and then the mixture was heated to 80 °C for 3 h. After the reaction was completed, pyridine was evaporated under vacuum to give crude **1**, which was purified by column chromatography with dichloromethane/methanol (30:1).

4-{4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic Acid Methylamide 1a

Yield 48.2%. ^{1}H NMR ($CDCl_3$): δ 3.04 (d, $J = 5$ Hz, 3 H), 6.98 (d, $J = 9$ Hz, 2 H), 7.18 (m, 1 H), 7.35 (m, 3 H), 7.53 (d, $J = 2$ Hz, 1 H), 7.71 (m, 2 H), 8.05 (s, 1 H), 8.34 (s, 1 H), 8.39 (d, $J = 4$ Hz, 1 H), 8.47 (d, $J = 6$ Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 25.98, 108.65, 114.01, 120.51, 121.44, 122.33, 123.11, 131.99, 137.03, 139.30, 147.83, 150.36, 152.44, 152.46, 163.77, 165.95. Mp: 204–205 °C.

4-[4-(3-*o*-Tolyl-ureido)-phenoxy]-pyridine-2-carboxylic Acid Methylamide 1b

Yield 54%. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3 H), 2.78 (d, $J = 5$ Hz, 3 H), 6.95 (m, 1 H), 7.15 (m, 5 H), 7.38 (d, $J = 3$ Hz, 1 H), 7.58 (d, $J = 8$ Hz, 2 H), 7.82 (d, $J = 8$ Hz, 1 H), 7.95 (s, 1 H), 8.49 (d, $J = 5$ Hz, 1 H), 8.75 (d, $J = 5$ Hz, 1 H), 9.15 (s, 1 H).^{13}C NMR (400 MHz, $CDCl_3$): δ 17.93, 26.03, 108.67, 113.98, 119.71, 121.20, 121.54, 122.81, 126.20, 127.70, 130.23, 137.34, 137.81, 147.32, 150.37, 152.45, 152.71, 163.82, 166.08. HRMS (ESI): m/z calcd. for $C_{21}H_{20}N_4NaO_3$ [M $+Na^+$]: 399.1428. Found: 399.1434. Mp: 189–190 °C.

4-{4-[3-(4-Nitro-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylic Acid Methylamide 1c

Yield 54.8%. ^{1}H NMR ($CDCl_3$): δ 2.78 (d, $J = 5$ Hz, 3 H), 7.15 (m, 1 H), 7.19 (d, $J = 9$ Hz, 2 H), 7.38 (d, $J = 3$ Hz, 1 H), 7.60 (d, $J = 8$ Hz, 2 H), 7.70 (d, $J = 9$ Hz, 2 H), 8.20 (d, $J = 9$ Hz, 2 H), 8.50 (d, $J = 5$ Hz, 1 H), 8.76 (d, $J = 5$ Hz, 1 H), 9.08 (s, 1 H), 9.50 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 26.03, 108.68, 114.05, 117.53, 120.49, 121.56, 125.19, 136.90, 141.05, 146.36, 147.96, 150.40, 152.05, 152.45, 163.80, 165.96. HRMS (ESI): m/z calcd. for $C_{20}H_{17}N_5NaO_5$ [M $+Na^+$]: 430.1122. Found: 430.1111. Mp: 240–241 °C.

4-{4-[3-(4-Methoxy-phenyl)-ureido]-phenoxy}-pyridine-2-carboxylicacimethylamide 1d

Yield 52.2%. ^{1}H NMR ($CDCl_3$): δ 2.78 (d, $J = 5$ Hz, 3 H), 3.72 (s, 3 H), 6.87 (d, $J = 9$ Hz, 2 H), 7.13 (m, 3 H), 7.37 (m, 3 H), 7.55 (d, $J = 9$ Hz, 2 H), 8.50 (d, $J = 6$ Hz, 2 H), 8.73 (d, $J = 7$ Hz, 2 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ25.95, 55.12, 108.59, 113.90, 113.95, 119.76, 120.04, 121.37, 132.60, 137.77, 147.19, 150.30, 152.37, 152.72, 154.46, 163.75, 166.01. HRMS (ESI): m/z calcd. for $C_{21}H_{20}N_4NaO_4$ [M $+Na^+$]: 415.1377. Found: 415.1382. Mp: 217–218 °C.

4-[4-(3-Thiazol-2-yl-ureido)-phenoxy]-pyridine-2-carboxylic Acid Methylamide 1e

Yield 62.5%. ^{1}H NMR ($CDCl_3$): δ 2.78 (d, $J = 5$ Hz, 3 H), 7.14 (m, 2 H), 7.19 (d, $J = 9$ Hz, 2 H), 7.38 (t, 2 H), 7.60 (t, 2 H), 8.50 (d, $J = 5$ Hz, 1 H), 8.76 (d, $J = 5$ Hz, 1 H), 9.11 (s, 1 H), 11.62 (br, 1 H).^{13}C NMR (400 MHz, $CDCl_3$): δ 26.32, 109.06, 112.82, 114.35, 120.91, 121.87, 136.73, 136.81, 137.13, 137.21, 148.45, 150.78, 152.26, 152.58, 160.00, 164.29, 166.21. HRMS (ESI): m/z calcd. for $C_{17}H_{15}N_5NaO_3S$ [M $+Na^+$]: 392.0788. Found: 392.0781. Mp: 231–233 °C.

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