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SHORT COMMUNICATION

Convenient amidation of carboxyl group of carboxyphenylboronic acids

Julia Nowak-Jary*

Faculty of Biological Sciences, University of Zielona Góra, ul. Szafrana 1, 65-516 Zielona Góra, Poland

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The use of catalysts in the activation of carboxyl groups towards nucleophilic attack and the protection of other functional groups by suitable protecting groups are standard and necessary procedures in amide bond formation. In contrast to the usual methods, various new compounds, amides of APTES ((3-aminopropyl)triethoxysilane, 3-triethoxysilylpropylamine) and carboxyphenylboronic acids, as well as the amides of aniline and carboxyphenylboronic acids, were obtained in good yields by a one-step synthesis under mild conditions without using any coupling reagents or additional catalysts.

Keywords: carboxyphenylboronic acids, amides, APTES, aniline, boronobenzanilides, amidation reaction

No simple general procedure for direct production of amides from free carboxylic acids and amines has yet been introduced. The thermal dehydration reaction between carboxylic acids and amines leading to amide bond formation occurs at very high temperatures (160 ℃ and higher) (Jursic & Zdravkovski, 1993). One widely used method uses acid chlorides as electrophiles that react with the amines; limitations of this method are due to the instability of many acid chlorides typically requiring hazardous reagents for their preparation. Another common means of forming amide bonds involves coupling reagents, such as carbodiimides or phosphonium salts, to activate and dehydrate carboxylic acid (Montalbetti & Falque, 2005). A widely known method involving coupling reagent, especially common in peptide synthesis, is the *N*-hydroxysuccinimide (HOSu) active ester method (Anderson et al., 1964) which uses dicyclohexylcarbodiimide (DCC) as the coupling reagent. However, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) is superior to DCC because of its high solubility in water and organic solvents, such as MeOH, CH_2Cl_2, and THF, and its functional simplicity (Sheehan et al., 1961).

The use of small amount (10 mole %) of boric acid and phenylboronic acid (PBA) (Mylavarapu et al., 2007) as well as their derivatives as catalysts in amidation reactions has also been reported. The highest yields (60–95 %) of products were obtained using the following PBA derivatives as catalysts: a series of fluorophenylboronic acids and 3,4-chlorophenylboronic acid (Tam et al., 2015), bromophenylboronic and iodophenylboronic acid (Al-Zoubi et al., 2008), tris(2,2,2-trifluoroethyl) borate (Lanigan et al., 2013), and 2-furanylboronic, 3-cyanophenylboronic and 2-thiophenylboronic acids (Tam et al., 2015). All the above-mentioned compounds were added as catalysts to the reaction mixture containing carboxylic acid and an amine. The PBA derivatives can also be applied in their immobilized form (Gu et al., 2014). Noda and Bode (2014) described a method, where acylboronate MIDA esters (MIDA = *N*-methyliminodiacetic acid) are substrates for the amidation reaction. In such compounds, the boron atom of the MIDA ester is substituted by the nitrogen atom of *O*-methylhydroxylamine. It is worth noting that the nucleophilic attack on the carbon atom of the carboxylic group on the aromatic ring is usually

*Corresponding author, e-mail: J.Nowak-Jary@wnb.uz.zgora.pl

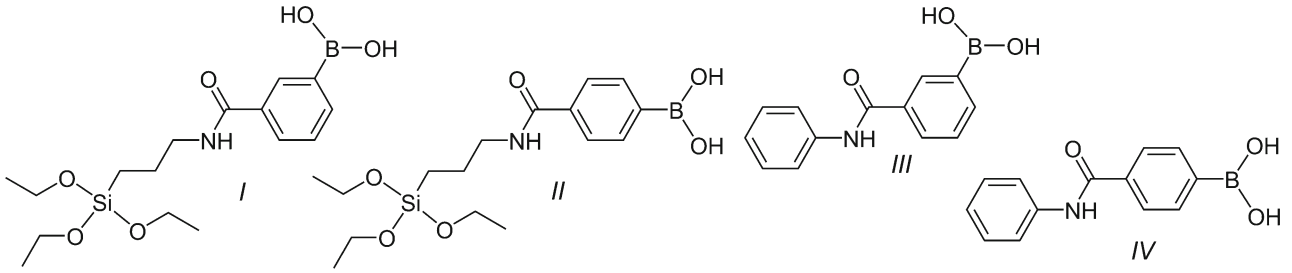

Fig. 1. Chemical structures of 3-{[3-(triethoxysilyl)propyl]carbamoyl}phenylboronic acid (*I*), 4-{[3-(triethoxysilyl)propyl]carbamoyl}phenylboronic acid (*II*), 3-(phenylcarbamoyl)phenylboronic acid (*III*), and 4-(phenylcarbamoyl)phenylboronic acid (*IV*).

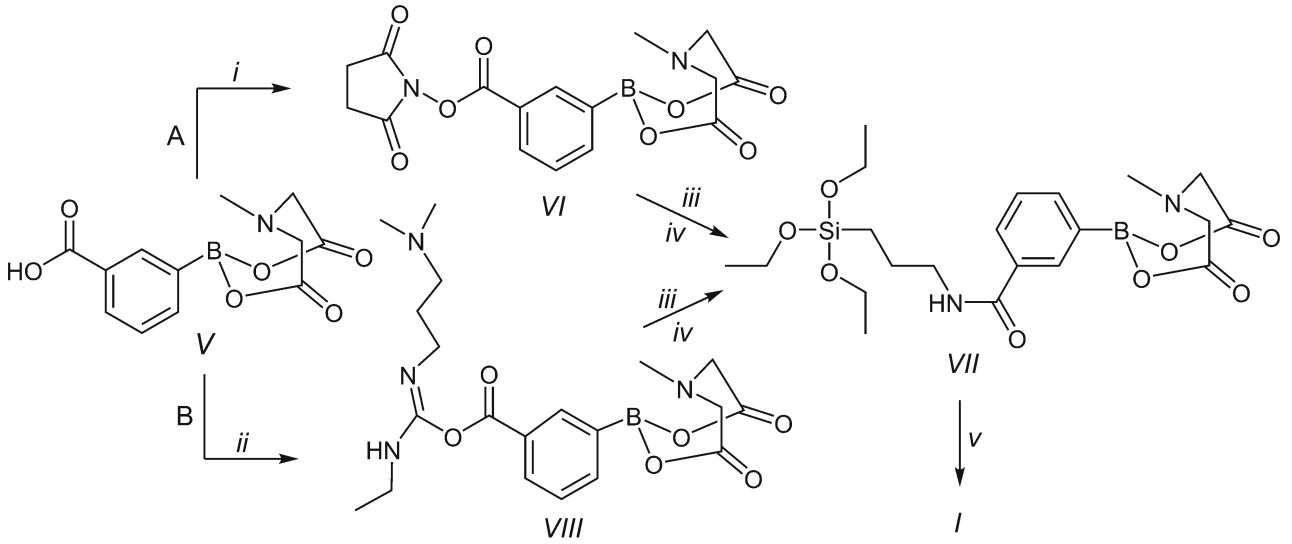

Fig. 2. Synthesis of amide *I* using compound *V* as the initial substrate and dicarbodiimides as coupling reagents. Reaction conditions: method A: *i*) DCC/HOSu, THF, 0 °C; method B: *ii*) EDC, MeOH, 25 °C; *iii*) APTES, MeOH, 25 °C; *iv*) aq. HCl, 25 °C; *v*) aq. NaOH, THF, 25 °C. Compound *II* was synthesized in a similar manner at the same conditions using 4-carboxyphenylboronic acid MIDA ester as the initial substrate.

hampered because of the higher electron density.

In this work, which is a part of a broader research concerning immobilization of carboxyphenylboronic acids (CPBA) on magnetic nanoparticles of Fe_3O_4, a convenient method for the synthesis of CPBA amides is reported. The following compounds were synthesized and characterized: 3-{[3-(triethoxysilyl)propyl]carbamoyl}phenylboronic acid (*I*), 4-{[3-(triethoxysilyl)propyl]carbamoyl}phenylboronic acid (*II*), 3-(phenylcarbamoyl)phenylboronic acid (*III*), and 4-(phenylcarbamoyl)phenylboronic acid (*IV*) (Fig. 1).

First, the amides containing (3-aminopropyl)triethoxysilane (3-triethoxysilylpropylamine) (APTES) were synthesized by two common methods: using DCC as the coupling reagent via active ester formation (method A); and using EDC as a reagent directly coupling carboxylic acid and amines (method B) (Fig. 2). 3-Carboxyphenylboronic acid MIDA ester (IUPAC name: 3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)benzoic acid) (*V*) and 4-carboxyphenylboronic acid MIDA ester (IUPAC name: 4-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)benzoic acid) (both esters are commercially available from Sigma–Aldrich) were used as initial substrates for the preparation of compounds *I* and *II*, respectively. Substrates with protected hydroxyl groups were used in order to avoid possible side reactions.

Final products in both cases were purified by column chromatography using ethyl acetate/hexane ($\varphi_r = 1 : 8$) as the eluent. The achieved overall yields of *I* and *II* (41 % and 43 %, respectively (method A) and 24 % and 26 %, respectively (method B)) were not satisfactory. Therefore, application of the reactions shown in Fig. 2 (methods A and B) to synthesize compounds *III* and *IV* was abandoned.

In recent years, reports on PBA as a capable catalyst in the amide bond formation process have occurred (Lundberg et al., 2014). PBA forms mixed anhydrides with carboxylic acids activating thereby the carboxyl moiety by reducing the electron density at the carbonyl function. This information was the basis of the assumption that two molecules of carboxyphenylboronic acid can form mixed anhydrides

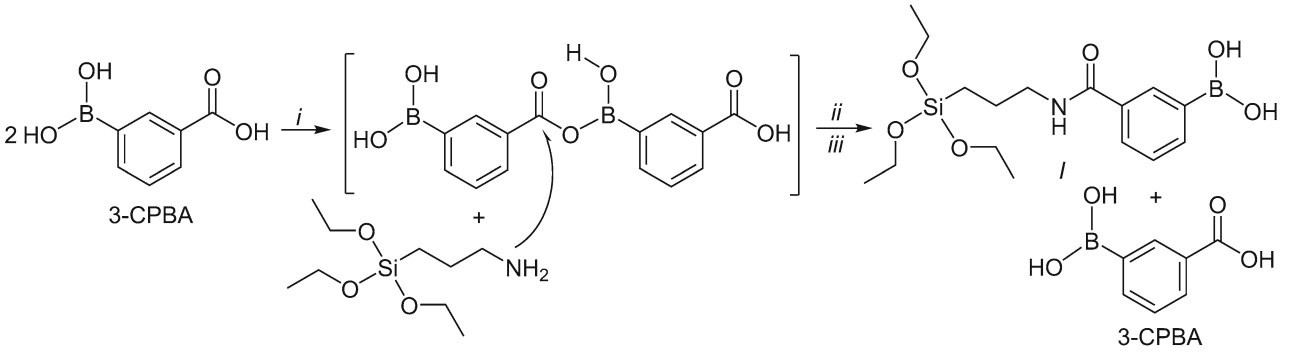

Fig. 3. Direct synthesis of amide *I* without the use of catalyst. Reaction conditions: *i*) toluene/MeOH, 4 Å molecular sieves, 60 °C, 1 h; *ii*) APTES, 60 °C, 24 h; *iii*) 0.5 M aqueous HCl, 25 °C. Compound *II* was synthesized in a similar manner under the same reaction conditions using 4-CPBA as the initial substrate.

Table 1. Synthesis of *I* and *II* by direct amidation of CPBA without additional catalysts

Compound	Solvent	T/ °C	Yield/%
I	MeOH	25	17
	MeOH	60	30
	Toluene/MeOH	25	27
	Toluene/MeOH	60	79
II	MeOH	25	19
	MeOH	60	33
	Toluene/MeOH	25	30
	Toluene/MeOH	60	83

(via COOH and $B(OH)_2$ groups), susceptible to nucleophilic attack of amines. Thus, it was decided to carry out the synthesis in accordance with Fig. 3, starting with 3-carboxyphenylboronic acid (3-CPBA) as the initial substrate. The 3-CPBA molecule obtained from the intermediary anhydride after the reaction with the amine reacts with another 3-CPBA molecule to afford the same anhydride and, via this repetition cycle, the synthesis proceeds to completion. This method was optimized and provided the best amidation results.

Since CPBA is poorly soluble in a number of organic solvents, apart from MeOH, the reactions were carried out in MeOH and, for comparison, in toluene with the addition of a small amount of MeOH to allow dissolution of CPBA. The substrates were also found to require higher temperatures (Table 1).

General method using N-hydroxysuccinimide active esters (method A)

THF (20 mL) was added to a mixture of *V* (277 mg, 1 mmol) and HOSu (115 mg, 1 mmol). The solution was cooled to 0 °C (ice bath) followed by the addition of DCC (206 mg, 1 mmol) dissolved in THF (10 mL), vigorous magnetic stirring for 1 h, and storage at 4 °C for 12 h. The white precipitate of dicyclohexylurea was removed by filtration using a glass funnel with filter paper and the excess of THF (approximately 25 mL) was evaporated on a rotary evaporator. Compound *VI* was crystallized by an addition of hexane and cooling to 4 °C. The obtained white crystals were filtered and dried under diminished pressure at ambient temperature to afford 262 mg (0.7 mmol, 70 %) of *VI*. The whole amount of the product was dissolved in MeOH (25 mL), APTES (0.180 mL, 0.77 mmol, 1.1 eq.) was added and the mixture was magnetically stirred at ambient temperature for 24 h. MeOH was evaporated on a rotary evaporator, the oily residue was suspended in 0.1 M aqueous HCl (20 mL) and the aqueous layer was extracted with ethyl acetate (EtOAc) (3 × 30 mL). The combined organic layers containing product *VII* were washed with distilled water (3 × 20 mL) until neutral pH, dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated on a rotary evaporator and the oily residue was dissolved in THF (10 mL) followed by the addition of 1 M aqueous NaOH (2 mL). The mixture was magnetically stirred at ambient temperature for 1 h and THF was evaporated on a rotary evaporator. Then, 1 M aqueous HCl (10 mL) was added to the resulting aqueous layer and product *I* was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with distilled water (3 × 20 mL) until neutral pH, dried with anhydrous $MgSO_4$ and filtered; the solvent was evaporated to afford the crude product which was purified on a column of silica gel using EtOAc/hexane ($\varphi_r = 1 : 8$) as the eluent) to yield the desired product *I* (151 mg, 41 %) as a white solid (m.p. 228–229 °C).

Product *II* (159 mg, 43 %) was obtained as a white solid (m.p. 205–206 °C) in a similar manner under the same conditions.

General method using EDC as a coupling reagent (method B)

A mixture of *V* (277 mg, 1 mmol) dissolved in MeOH (5 mL) and EDC hydrochloride (192 mg, 1 mmol) dissolved in MeOH (15 mL) was magneti-

Table 2. Spectral data of newly prepared compounds

Compound	Spectral data
I	FTIR (KBr), $\tilde{\nu}$/cm^{-1}: 3434 (NH, OH), 1544 (NH), 1637 (C═O), 1019 (Si—O), 780 (Ph) ^{1}H NMR (500 MHz, DMSO-d_6), δ: 0.79 (m, 2H, $SiCH_2$), 1.25 (t, 9H, 3 × CH_3, J = 6.9 Hz), 1.96 (m, 2H, CH_2), 2.56 (m, 2H, NCH_2), 4.10 (q, 6H, 3 × OCH_2, J = 7.1 Hz), 6.96 (t, 1H, H-Ph, J = 7.8 Hz), 7.24 (d, 1H, H-Ph, J = 7.8 Hz), 7.36 (d, 1H, H-Ph, J = 7.3 Hz), 7.31 (s, 1H, H-Ph), 7.96 (s, 2H, 2 × OH), 8.95 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6), δ: 8.23 ($SiCH_2$), 19.48 (3 × CH_3) 28.41 (CH_2), 46.18 (NCH_2), 56.3 (3 × OCH_2), 128.49 (Ph), 130.51 (Ph), 131.20 (Ph), 131.57 (Ph), 135.85 (Ph), 139.14 (Ph), 168.38 (C═O) HRMS (ESI), m/z (I_r/%) (found/calc.): 370.237/369.234 ([M + H]$^+$, $C_{16}H_{28}O_6NSiB$, 22.8)
II	FTIR (KBr), $\tilde{\nu}$/cm^{-1}: 3434 (NH, OH), 1544 (NH), 1640 (C═O), 1062 (Si—O), 830 (Ph) ^{1}H NMR (500 MHz, DMSO-d_6), δ: 0.78 (m, 2H, $SiCH_2$), 1.25 (t, 9H, 3 × CH_3, J = 6.9 Hz), 1.96 (m, 2H, CH_2), 2.61 (m, 2H, NCH_2), 4.10 (q, 6H, 3 × OCH_2, J = 7.2 Hz), 6.94 (d, 2H, H-Ph, J = 8.7 Hz), 7,18 (d, 2H, H-Ph, J = 8.9 Hz), 7.94 (s, 2H, 2 × OH), 9.00 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6), δ: 8.23 ($SiCH_2$), 19.48 (3 × CH_3) 28.41 (CH_2), 46.18 (NCH_2), 56.30 (3 × OCH_2), 129.32 (1C, Ph), 130.10 (1C, Ph), 134.92 (2C, Ph), 138.53 (2C, Ph), 168.50 (C═O) HRMS (ESI), m/z (I_r/%) (found/calc.): 370.239/369.234 ([M + H]$^+$, $C_{16}H_{28}O_6NSiB$, 26.4)
III	FTIR (KBr), $\tilde{\nu}$/cm^{-1}: 3430 (NH, OH), 1540 (NH), 1680 (C═O) 780, 750 (Ph) ^{1}H NMR (500 MHz, DMSO-d_6), δ: 7.05 (m, 1H, H-Ph), 7.21 (m, 2H, H-Ph), 7.40 (m, 2H, H-Ph), 7.62 (t, 1H, H-Ph, J = 7.7 Hz), 7.67 (d, 1H, H-Ph, J = 1.37 Hz), 8.09 (d, 1H, H-Ph, J = 7.14 Hz), 8.15 (s, 2H, 2 × OH), 8.45 (s, 1H, H-Ph), 10.28 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6), δ: 120.30 (2C, Ph), 123.54 (1C, Ph), 127.57 (1C, Ph), 128.28 (1C, Ph), 128.51 (2C, Ph), 131.66 (1C, Ph), 132.69 (1C, Ph), 134.94 (1C, Ph), 135.66 (1C, Ph), 139.11 (1C, Ph), 168.54 (C═O) HRMS (ESI), m/z (I_r/%) (found/calc.): 242.020/241.016 ([M + H]$^+$, $C_{13}H_{12}O_3NB$, 35.2)
IV	FTIR (KBr), $\tilde{\nu}$/cm^{-1}: 3430 (NH, OH), 1542 (NH), 1678 (C═O) 830, 750 (Ph) ^{1}H NMR (500 MHz, DMSO-d_6), δ: 7.07 (m,1H, H-Ph), 7.25 (m, 2H, H-Ph), 7.42 (m, 2H, H-Ph), 7.93 (d, 2H, H-Ph, J = 7.9 Hz), 8.00 (d, 2H, H-Ph, J = 8.2 Hz), 8.13 (s, 2H, 2 × OH), 9.83 (s, 1H, NH) ^{13}C NMR (500 MHz, DMSO-d_6), δ: 121.20 (2C, Ph), 124.96 (1C, Ph), 129.51 (2C, Ph), 130.28 (2C, Ph), 131.21 (2C, Ph), 134.72 (1C, Ph), 136.16 (1C, Ph), 139.11 (1C, Ph), 168.48 (C═O) HRMS (ESI), m/z (I_r/%) (found/calc.): 242.018/241.016 ([M + H]$^+$, $C_{13}H_{12}O_3NB$, 37.6)

cally stirred at ambient temperature for 2 h to afford *VIII*. Then, the same reaction steps and conditions as described in method A were applied to afford *VII* and finally *I* (89 mg, 24 %).

Product *II* was obtained as a white solid (96 mg, 26 %) in a similar manner under the same conditions.

Optimized general method for direct amidation of CPBA carbocyl group using APTES

Toluene (25 mL) and activated 4 Å molecular sieve beads (0.5 g) were added to a solution of 3-CPBA or 4-CPBA (166 mg, 1 mmol) in MeOH (3 mL) and the mixture was magnetically stirred at 60 ℃ for 1 h. APTES (0.468 mL, 2 mmol) was then added and the mixture was stirred at 60 ℃ for additional 24 h followed by the filtration through a pad of Celite®545 and evaporation of the solvent on a rotary evaporator. The oily residue was suspended in 0.5 M aqueous HCl (20 mL) and the product was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with distilled water (3 × 20 mL) until neutral pH, dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated to afford *I* (292 mg, 79 %) or *II* (306 mg, 83 %) as white solid with purity higher than 95 % (according to ^{1}H NMR data).

Application of this optimized method to benzoic acid revealed that the amidation reaction did not proceed, confirming thus that the boronic acid group ($B(OH)_2$) plays the activating role.

Similarly, this optimized direct amidation method was applied to the synthesis of compounds *III* and *IV* using aniline as a nucleophile instead of APTES; however, a small excess of CPBA (1.1 eq.) in relation to aniline was used to obtain better yields. Considering the significantly lower reactivity of aniline compared to benzylamine and aliphatic amines (including APTES), the resulting yields of 39 % and 42 % of products *III* (m.p. 245–246 ℃) and *IV* (m.p. 222–223 ℃), respectively, were considered satisfactory. Spectral data of the new compounds *I*–*IV* are shown in Table 2.

Chemicals were of analytical grade and used as received without further purification. All reagents and activated 4 Å molecular sieve were purchased from Sigma–Aldrich (Poland), and organic solvents were purchased from Avantor Performance Materials (Poland). TLC silica gel 60 plates and silica gel 60 (0.015–0.040 mm) for column chromatography were obtained from Merck Millipore (Poland).

^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Varian Unity 500 Plus spectrometer (USA) using TMS as the internal standard. FTIR spectra (KBr pellet technique) were measured on a Nicolet iS50 FTIR spectrometer (USA) in the range of 400–4000 cm^{-1}. HRMS spectra (ESI-Q-TOF-MS) were obtained on a Bruker micrOTOF-Q spectrometer

(Germany). Melting points were recorded on a Kofler hot block and are uncorrected.

In conclusion, the new CPBA amides were obtained by a very simple method without using any coupling reagents or additional catalysts. So far, catalytic potential of the amidation reaction of CPBA has not been studied. Likewise, there are also no reports regarding the direct amidation of the carboxyl group of unprotected CPBA in a solution. It was demonstrated in this study that CPBA is a suitable substrate for the amidation reaction, and also an excellent catalyst; the boronic part of one molecule activates the carboxyl group of another molecule of the same compound. Therefore, there is no need to use any additional catalysts or coupling reagents. Because only the substrates participate in the reaction, the formation of by-products is eliminated. The excess of amine and a small amount of unreacted CPBA are removed by simple extraction. The presented method can be used as a general method for the synthesis of specific CPBA amides.

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