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Synthesis of Naphthoxazinones in a One-Pot Two-Step Manner by the Application of Propylphosphonic Anhydride (T3P®)

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Abstract: A sequential one-pot two-step protocol has been elaborated for the synthesis of naphthoxazinones from 2-naphthol, methyl carbamate, and aromatic aldehydes. First, a three-component reaction was optimized with the dehydrating additive propylphosphonic anhydride (T3P®), resulting in 1-carbamatoalkyl 2-naphthols in good to excellent yields. Following the successful multicomponent approach, intramolecular acylation was performed at high temperature, again with the contribution of T3P®, resulting in naphthoxazinone derivatives in moderate yields. These two steps were optimized together in one-pot as well, and the sequential rise in the requisite temperature eventuated the optimal procedure for the multistep cascade.

Keywords: multicomponent reaction; 1-carbamatoalkyl 2-naphthols; naphthoxazinones; T3P®; mechanism

1. Introduction

Multicomponent reactions play a significant role in organic synthesis [1], medicinal chemistry [2], and materials science [3]. In this highly atom-efficient process, three or more starting materials react in a single operational step to form the product. Therefore, large libraries of organic molecules can be readily produced in this way. Hitherto, a vast amount of significant multicomponent reactions have been discovered from the Strecker α-aminonitrile synthesis to the Groebke–Blackburn–Bienaymé reaction.

1-Carbamatoalkyl 2-naphthols, important intermediates of biologically active compounds, can be easily prepared in a three-component reaction of 2-naphthol, methyl carbamate, and aromatic aldehydes (Scheme 1). Over the past decade, this condensation reaction has been investigated in the presence of various catalysts, such as cerium ammonium nitrate [4], ionic liquids [5–12], magnesium 2,2,2-trifluoroacetate [13], a non-ionic surfactant, Tween® 20 [14], sulfamic acid-functionalized magnetic nanoparticles [15], tin tetrachloride [16], saccharin sulfonic acid [17], nanocrystalline TiO_2–$HClO_4$ [18], magnesium hydrogen sulphate [19], silica perchloric acid [20], trityl chloride [21], silica-supported sodium hydrogen sulphate [22], and P_2O_5 supported on SiO_2 [23]. The 1-carbamatoalkyl 2-naphthols can be converted further by hydrolysis or a ring closure. The hydrolyzed products 1-aminoalkyl-2-naphthols exhibit cardiovascular activity [24], while naphthalene-condensed 1,3-oxazin-3-ones possess an antibacterial effect [25].
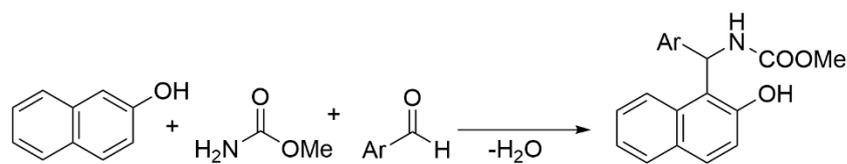
Scheme 1. Schematic illustration of the Betti-type three-component reaction of 2-naphthol, methyl carbamate, and aldehydes.

Propylphosphonic anhydride (T3P®) was discovered and first used in peptide chemistry as a coupling agent by Wissmann and Kleiner [26]. Later, this effective water scavenger reagent was applied in several functional group transformations, rearrangements, carbon–carbon bond formations, the synthesis of various heterocycles, and organophosphorus compounds [27–29]. Furthermore, one should note that T3P® has several advantageous properties including good solubility in organic solvents, low toxicity, and broad functional group tolerance. The forming by-products are water-soluble and can be easily removed by alkaline extraction. Our research group has so far successfully applied the T3P®-reagent in multicomponent and one-pot cascade reactions [30–34]. By continuing our work in this area, we herein report a T3P®-mediated three-component Betti-type reaction of 2-naphthol, methyl carbamate, and aromatic aldehydes.

2. Materials and Methods

2.1. General

Melting points were determined on a Büchi B-540 capillary melting point apparatus (Essen, Germany) or on a Jasco SRS OptiMelt melting point apparatus (Sunnyvale, CA, USA) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 303 K on a Bruker Avance III HD (600 and 150 MHz for ^{1}H and ^{13}C NMR spectra, respectively, a Bruker Avance III (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) (Billerica, MA, USA), or a Varian Unity Inova 300 MHz spectrometer (300 and 75 MHz for ^{1}H and ^{13}C NMR spectra, respectively) (Oxford, UK). DMSO-d_6 and/or CDCl$_3$ was used as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. Mass spectra were recorded on a Bruker O-TOF MAXIS Impact mass spectrometer coupled to a Dionex Ultimate 3000 RS HPLC system (Thermo Fischer Scientific, Waltham, MA, USA) with a diode array detector. The reactions were followed by analytical thin-layer chromatography on silica gel 60 F$_{254}$ and HPLC–MS chromatography on a Shimadzu LC-MS-2020 apparatus. Purifications by flash chromatography were carried out using Merck 107736 silica gel 60 H (Darmstadt, Germany) using a hexane–ethyl acetate, hexane-dichloromethane, or dichloromethane-methanol solvent system. All reagents were purchased from commercial sources (Merck, Darmstadt, Germany, Fluorochem, Hadfield, UK, Combi-Blocks, San Diego, CA, USA). Analytical samples of new compounds were obtained by recrystallization from the solvents or solvent mixtures given below in parentheses. The ^{1}H and ^{13}C NMR spectra of the compounds can be found in the Supplementary Material.

2.2. General Procedure for the Synthesis of 2-Hydroxynaphthalen-1-yl-carbamates (**4a–i**)

In a round-bottom flask, 144 mg of 2-naphthol (**1**, 1.0 mmol) and 83 mg of methyl carbamate (**2**, 1.1 mmol, 1.1 equiv.) were dissolved in 5.0 mL of toluene with vigorous stirring. The appropriate aromatic aldehyde (**3a–i**, 1.1 mmol, 1.1 equiv.) was added to the mixture, followed by the addition of T3P® (50% ethyl acetate solution, 0.66 mL, (1.1 mmol, 1.1 equiv.)). The reaction mixture was stirred for 30 min at 80 °C. After the end of the reaction, 20 mL of ethyl acetate was added and washed with 15 mL of water and 15 mL of saturated NaHCO$_3$. The organic phase was separated, dried (MgSO$_4$), filtered, evaporated to silica, and purified by flash column chromatography with hexane–ethyl acetate.

Methyl ((3-fluorophenyl)(2-hydroxynaphthalen-1-yl)methyl)carbamate (**4a**). Yield: 289 mg, (89%); white crystals; mp. 229–232 °C (ethyl acetate). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.18 (b, 1H, OH), 7.91 (b, 1H, Ar-H), 7.82 (m, 1H, Ar-H), 7.78 (d, J = 8.7 Hz, 1H, Ar-H), 7.77 (b, 1H, NH), 7.41 (m, 1H, Ar-H), 7.29 (m, 2H, Ar-H), 7.21 (d, J = 8.8 Hz, 1H, Ar-H), 7.04 (m, 1H, Ar-H), 7.02 (m, 2H, Ar-H), 6.87 (bd, J = 8.8 Hz, 1H, CH), 3.58 (s, 3H, CH$_3$) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.3 (C=), 156.8 (=CO), 153.2 (C=), 145.8 (C=), 132.1 (C=), 130.3 (=CH), 129.8 (=CH), 128.8 (=CH), 128.6 (C=), 126.9 (=CH), 123.2 (=CH), 122.8 (=CH), 122.4 (=CH), 118.60 (C=), 113.3 (=CH), 112.9 (=CH), 51.9 (CH$_3$), 50.2 (CH) ppm. HRMS calcd. for C$_{19}$H$_{15}$FNO$_3$ [M − H]$^-$: 324.1035; found: 324.1015.

Methyl ((2-hydroxynaphthalen-1-yl)(4-phenoxyphenyl)methyl)carbamate (**4b**). Yield: 239 mg, (60%); white crystals; mp. 201–203 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.16 (s, 1H, OH), 7.96 (m, 1H, Ar-H), 7.82 (d, J = 7.81 Hz, 1H, Ar-H), 7.76 (d, J = 8.84 Hz, 1H, Ar-H), 7.68 (s, 1H, NH), 7.42 (m, 1H, Ar-H), 7.31 (m, 2H, Ar-H), 7.29 (m, 1H, Ar-H), 7.27 (m, 3H, Ar-H), 7.10 (m, 1H, Ar-H), 6.96 (m, 4H, Ar-H), 6.83 (d, J = 7.8 Hz, 1H, CH), 3.57 (s, 3H, CH$_3$) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.0 (=CO), 156.7 (C=), 155.2 (C=), 153.1 (C=), 137.6 (=CH), 132.2 (C=), 130.1 (=CH), 129.5 (=CH), 128.7 (=CH), 128.5 (C=), 127.9 (=CH), 126.7 (C=), 123.9 (=CH), 123.1 (=CH), 122.7 (=CH), 118.9 (=CH), 118.6 (=CH), 118.4 (=CH), 51.8 (CH$_3$), 50.3 (CH) ppm. HRMS calcd. for C$_{25}$H$_{20}$NO$_4$ [M − H]$^-$: 398.1392; found: 398.1373.

Methyl ((3-chloro-4-fluorophenyl)(2-hydroxynaphthalen-1-yl)methyl)carbamate (**4c**). Yield: 309 mg, (86%); white crystals; mp. 238–240 °C (decomp). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H, OH), 7.92 (d, J = 8.36 Hz, 1H, Ar-H), 7.80 (m, 3H, Ar-H, NH), 7.41 (m, 2H, Ar-H), 7.30 (m, 2H, Ar-H), 7.16 (m, 2H, Ar-H), 6.84 (d, J = 7.80 Hz, 1H, CH), 3.58 (s, 3H, CH$_3$) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.2 (C=), 156.7 (=CO), 154.8 (C=), 153.2 (=CH), 140.5 (=CH), 132.0 (C=), 129.9 (=CH), 128.8 (=CH), 128.5 (C=) 128.1 (=CH), 126.9 (=CH), 122.9 (C=), 122.8 (=CH), 119.3 (C=), 119.1 (C=), 118.6, (=CH), 116.6 (=CH), 51.9 (CH$_3$), 49.8 (CH) ppm.

Methyl ((2-hydroxynaphthalen-1-yl)(phenyl)methyl)carbamate (**4d**). Yield: 249 mg, (81%); white crystals; mp. 215–217 °C, (Lit.: 217–218 °C) [22]. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.10 (s, 1H, OH), 7.92 (d, J = 8.6 Hz, 1H, Ar-H), 7.79 (dd, J = 12.4, 8.5 Hz, 2H, Ar-H), 7.65 (d, J = 8.8 Hz, 1H, NH), 7.40 (t, J = 7.7 Hz, 1H), 7.32–7.15 (m, 7H, Ar-H), 6.86 (d, J = 8.9 Hz, 1H, CH), 3.58 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.0 (=CO), 153.3 (=CH), 142.8 (=CH), 132.5 (C=), 129.7 (=CH), 129.0 (=CH), 128.8 (C=), 128.5 (=CH two signals), 127.0 (C=), 126.8 (=CH), 126.5 (=CH two signals), 123.5 (C=), 123.0 (=CH), 119.3 (C=), 118.8 (=CH), 52.1 (CH$_3$), 50.9 (CH). HRMS calcd. for C$_{19}$H$_{16}$NO$_3$ [M − H]$^-$: 306.1124; found: 306.1135.

Methyl ((2-hydroxynaphthalen-1-yl)(3-phenoxyphenyl)methyl)carbamate (**4e**). Yield: 359 mg, (90%); white crystals; mp. 183–185 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12 (s, 1H, OH), 7.90 (d, J = 8.3 Hz, 1H, Ar-H), 7.84–7.64 (m, 3H, Ar-H, NH), 7.45–7.17 (m, 6H, Ar-H), 7.10 (t, J = 7.3 Hz, 1H, Ar-H), 7.02–6.83 (m, 5H, Ar-H), 6.79 (d, J = 8.0 Hz, 1H, CH), 3.56 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.4 (=CO), 157.0 (=CH), 156.7 (C=), 153.4 (=CH), 145.4 (=CH), 132.4 (C=), 130.4 (C=), 130.2 (=CH two signals), 129.9 (C=), 129.02 (C=), 128.8 (=CH), 127.0 (=CH), 123.7 (=CH two signals), 123.5 (C=), 123.0 (=CH), 121.7 (C=), 119.0 (=CH), 118.8 (=CH), 118.7 (=CH), 117.1 (=CH), 116.8 (=CH), 52.1 (CH$_3$), 50.6 (CH). HRMS calcd. for C$_{25}$H$_{30}$NO$_4$ [M − H]$^-$: 398.1392; found: 398.1370.

Methyl ((3,4-difluorophenyl)(2-hydroxynaphthalen-1-yl)methyl)carbamate (**4f**). Yield: 244 mg, (71%); white crystals; mp. 201–202 °C ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.30 (s, 1H, OH), 7.93 (d, J = 8.6 Hz, 8.44 Hz, Ar-H), 7.80 (m, 3H, Ar-H, NH), 7.42 (m, 1H, Ar-H), 7.29 (m, 4H, Ar-H), 7.00 (m, 1H, Ar-H), 6.83 (s, 1H, CH), 3.58 (s, 3H, CH$_3$) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 156.7 (=CO), 153.3 (=CH), 150.6 (C=), 149.4 (C=), 149.3 (C=), 140.5 (C=), 132.06 (C=), 129.8 (=CH), 128.8 (=CH), 128.5 (C=), 126.9 (=CH), 123.0 (=CH), 118.7 (=CH), 118.3 (=CH), 117.2 (=CH), 115.1 (=CH), 51.9 (CH$_3$), 50.0 (CH) ppm. HRMS calcd. for C$_{19}$H$_{14}$NO$_3$ [M − H]$^-$: 342.0947; found: 342.0920.

Methyl ((2-hydroxynaphthalen-1-yl)(pyridin-3-yl)methyl)carbamate (**4g**). Yield: 225 mg, (73%); white crystals; mp. 207–210 °C, (Lit.: 207–209 °C) [8]. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H, NH), 8.45 (m, 1H, Ar-H), 8.38 (m, 1H, NH), 7.96 (d, *J* = 8.53 Hz, 1H, Ar-H), 7.81 (m, 3H, Ar-H), 7.62 (d, *J* = 7.96 Hz, 1H, Ar-H), 7.42 (m, 1H, Ar-H), 7.31 (m, 2H, Ar-H), 7.21 (d, *J* = 8.84 Hz, 1H, Ar-H), 6.89 (d, *J* = 8.44 Hz, 1H, CH), 3.58 (s, 3H, CH$_3$) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 156.8 (=CO), 153.2 (C=), 147.8 (=CH, two signals), 137.9 (C=), 134.0 (=CH), 132.0 (C=), 129.9 (=CH), 128.8 (=CH), 128.5 (=CH), 126.9 (C=), 123.4 (=CH), 122.9 (=CH), 122.8 (=CH), 118.6 (=CH), 118.1 (C=), 51.9 (CH$_3$), 48.9 (CH) ppm. HRMS calcd. for $C_{18}H_{17}N_2O_3$ [M + H]$^+$: 307.1233; found: 307.1231.

Methyl ((2-hydroxynaphthalen-1-yl)(thiazol-4-yl)methyl)carbamate (**4h**). Yield: 242 mg, (77%); white chrystals; mp. 208–210 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.05 (s, 1H, OH), 8.92 (m, 1H, Ar-H), 8.06 (d, *J* = 8.45 Hz, 1H, OH), 7.78 (m, 3H, Ar-H), 7.40 (m, 2H, Ar-H), 7.27 (m, 1H, Ar-H), 7.15 (d, *J* = 8.84 Hz, 1H, Ar-H), 6.92 (d, *J* = 8.52 Hz, 1H, Ar-H), 3.56 (s, 3H) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.0 (C=), 156.4 (=CO), 153.8 (=CH), 153.1 (C=), 132.3 (C=), 129.4 (=CH), 128.6 (=CH), 128.4 (=CH), 126.5 (C=), 123.2 (C=), 122.6 (=CH), 118.6 (=CH), 118.4 (=CH), 114.5 (=CH), 51.8 (CH$_3$), 48.9 (CH) ppm. HRMS calcd. for $C_{16}H_{15}N_2O_3S$ [M + H]$^+$: 315.0797; found: 315.0799.

Methyl ((2-hydroxynaphthalen-1-yl)(quinolin-4-yl)methyl)carbamate (**4i**). Yield: 236 mg, (66%); white crystals; mp. 250–252 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.15 (s, 1H, OH), 8.87 (d, *J* = 4.44 Hz, 1H, Ar-H), 8.18 (m, 1H, Ar-H), 8.01 (m, 2H, Ar-H), 7.93 (m, 1H, Ar-H), 7.79 (m, 2H, Ar-H), 7.67 (t, *J* = 7.56 Hz, 1H, Ar-H), 7.58 (d, *J* = 4.26 Hz, 1H, Ar-H), 7.45 (t, *J* = 7.57 Hz, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 7.35 (d, *J* = 7.92 Hz, 1H, Ar-H), 7.27 (m, 1H, Ar-H), 7.17 (m, 1H, CH), 3.59 (s, 3H, CH$_3$) ppm. ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.5 (C=), 156.7 (C=), 153.5 (=CO), 150.3 (=CH), 148.1 (=CH), 132.7 (C=), 130.2 (=CH), 130.0 (=CH), 129.1 (=CH), 129.0 (=CH), 128.7 (C=), 126.9 (C=), 126.6 (=CH), 126.3 (C=), 123.6 (=CH), 123.0 (C=), 122.8 (=CH), 120.0 (=CH), 118.7 (=CH), 117.1 (=CH), 51.9 (CH$_3$), 48.8 (CH) ppm. HRMS calcd. for $C_{22}H_{19}N_2O_3$ [M + H]$^+$: 359.1390; found: 359.1396.

2.3. Ring-Closing Reaction from methyl ((2-hydroxynaphthalen-1-yl)(phenyl)methyl)carbamate (*4d*) to naphta[1,2]oxazinone Derivatives (*5d*)

In a Schlenk tube, 200 mg of ((2-hydroxynaphthalen-1-yl)(phenyl)methyl)carbamate (**4d**, 0.65 mmol) was dissolved in 10 mL of toluene, followed by the addition of T3P® (50% ethyl acetate solution, 0.78 mL, (1.30 mmol, 2.0 equiv.)). The reaction mixture was heated in an oil bath at 160 °C and stirred for 60 min. After the end of the reaction, 15 mL of water and 15 mL of saturated NaHCO$_3$ were added, and the organic phase was separated, dried (MgSO$_4$), filtered, evaporated to silica, and purified by flash column chromatography with hexane–ethyl acetate. The product was retained in 75% yield (134 mg) as a white solid.

2.4. General Procedure for the Synthesis of naphta[1,2]oxazinones (*5a*–*f*)

We have investigated six reaction pathways (**A**–**F**) to the one-pot ring-closing synthesis of naphtha[1,2-*e*]oxazinone derivatives. It was found that the most effective pathway was **E1**, **E2** under microwave (MW) conditions. In regard to the optimization results of the one-pot synthesis, we used pathway **E1**, **E2** for the synthesis of naphta[1,2-*e*]oxazinones.

In a microwave (MW) vial, 100 mg of 2-naphthol (**1**, 0.69 mmol) and 57 mg of methyl carbamate (**2**, 0.76 mmol, 1.1 equiv.) were dissolved in 7 mL of toluene. The appropriate aromatic aldehyde (**3a**–**f**, 0.76 mmol, 1.1 equiv.) was added to the mixture, followed by the addition of T3P® (50% ethyl acetate solution, 1.29 mL, (2.15 mmol, 3.1 equiv.)). The vial was sealed, and it was irradiated in a MW reactor at 80 °C for 15 min. After 15 min, the temperature was heated to 160 °C and the mixture was stirred for 35 min. The reaction was followed by adding 10 mL of water and 10 mL of saturated NaHCO$_3$, and the organic phase was separated, dried (MgSO$_4$), filtered, and evaporated to silica. The material evaporated to silica was purified by flash column chromatography with hexane-ethyl acetate.

1-(3-Fluorophenyl)-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (**5a**). Yield: 108 mg (53%), white crystals; mp. 218–221 °C (*i*-Pr$_2$O), (Lit.: 218–220 °C) [35]. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.94 (m, 1H, NH) 8.01–7.10 (m, 10 H, Ar-H), 6.27 (m, 1H, CH) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 164.5 (=CO), 161.2 (C=), 149.9 (=CH), 148.2 (=CH), 146.1 (C=), 131.8 (C=), 131.1 (=CH), 129.5 (=CH), 129.4 (=CH), 128.2 (=CH), 125.9 (=CH), 123.7 (=CH), 123.6 (C=), 117.6 (=CH), 115.5 (=C), 114.5 (C=), 114.1 (=CH), 53.8 (CH) ppm. HRMS calcd. for C$_{18}$H$_{13}$NO$_2$F [M + 1]$^+$: 294.0924; found: 294.0936.

1-(4-Phenoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (**5b**). Yield: 59 mg, (23%), white crystals; mp. 205–206 °C (*i*-Pr$_2$O). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.87–7.84 (m, 2H, Ar-H, NH), 7.55–6.94 (m, 14H, Ar-H), 6.08 (s, 1H, CH) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ 157.9 (=CO), 156.7 (C=), 150.8 (C=), 147.8 (C=), 136.5 (C=), 131.3 (C=), 130.8 (=CH), 130.0 (=CH two signals), 129.6 (C=), 129.1 (=CH), 128.7 (=CH two signals), 127.7 (=CH), 125.5 (=CH), 124.0 (=CH), 123.1 (=CH), 119.6 (=CH), 119.3 (=CH two signals), 117.3 (=CH), 112.9 (C=), 55.6 (CH) ppm. HRMS calcd. for C$_{24}$H$_{18}$NO$_3$ [M + H]$^+$: 368.1281; found: 368.1294.

1-(3-Chloro-4-fluorophenyl)-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (**5c**). Yield: 95 mg (42%), white crystals; mp. 214–216 °C (*i*-Pr$_2$O). ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.92 (d, *J* = 3Hz, 1H, NH), 8.02–7.20 (m, 9H, Ar-H), 6.30 (d, *J* = 3Hz, 1H, CH) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 159.0 (=CO), 155.8 (C=), 149.7 (=CH), 148.3 (C=), 141.3 (C=), 131.3 (=CH), 130.1 (=CH), 129.4 (=CH), 128.3 (=CH), 125.9 (=CH), 123.7 (=CH), 120.5 (C=), 120.3 (C=), 118.4 (C=), 118.2 (C=), 117.6 (=CH), 113.8 (=CH), 53.2 (CH) ppm. HRMS calcd. for C$_{18}$H$_{12}$NO$_2$FCl [M + 1]$^+$: 328.0535; found: 328.0547.

1-Phenyl-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (**5d**). Yield: 134 mg (75%), white crystals, mp. 217–223 °C (*i*-Pr$_2$O), (Lit.: 218–220 °C) [36]. ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.88 (s, 1H, NH), 7.99–7.26 (m, 11H, Ar-H), 6.21 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 150.0 (=CO), 148.1 (C=), 143.6 (=CH), 131.1 (C=), 130.9 (=CH), 129.6 (=CH), 129.6 (=CH), 129.3 (=CH), 128.7 (=CH), 128.0 (=CH), 127.7 (=CH), 125.8 (C=), 123.8 (=CH), 117.6 (=CH), 114.8 (C=), 54.5 (CH) ppm. HRMS calcd. for C$_{18}$H$_{14}$NO$_2$ [M + H]$^+$: 276.1019; found: 276.1029.

1-(3-Phenoxyphenyl)-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (**5e**). Yield: 105 mg (41%), white crystals; mp. 210–211 °C (*i*-Pr$_2$O). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.85–7.83 (m, 2H, Ar-H, NH), 7.53–6.79 (m, 14 H, Ar-H), 6.03 (s, 1H, CH) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 158.3 (=CO), 156.7 (C=), 150.3 (C=), 147.9 (C=), 143.8 (C=), 131.2 (C=), 131.0 (=CH), 130.9 (=CH), 130.1 (=CH two signals), 129.5 (C=), 129.1 (=CH), 127.7 (=CH), 125.5 (=CH), 123.9 (=CH), 123.0 (=CH), 121.7 (=CH), 119.3 (=CH), 118.6 (=CH), 117.6 (=CH), 117.3 (=CH), 112.4 (C=), 56.1 (CH) ppm. HRMS calcd. for C$_{24}$H$_{18}$NO$_3$ [M + H]$^+$: 368.1281; found: 368.1295.

1-(3,4-difluorophenyl)-1H-naphtho[1,2-e][1,3]oxazin-3(2H)-one (**5f**). Yield: 102 mg (47%), white crystals; mp. 220–223 °C (*i*-Pr$_2$O). ^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ 8.93 (s, 1H, NH), 8.01–7.08 (m, 9H, Ar-H), 6.29 (s, 1H, CH) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$) δ 149.8 (=CO), 148.2 (C=), 141.1 (C=), 131.3 (=CH), 131.1 (=CH), 129.5 (C=), 129.4 (=CH), 128.2 (=CH), 125.9 (=CH), 124.4 (C=), 123.7 (=CH), 119.0 (=CH), 118.8 (C=), 117.6 (=CH), 117.2 (C=), 117.0 (=CH), 113.8 (C=), 53.4 (CH) ppm. HRMS calcd. for C$_{18}$H$_{12}$NO$_2$F$_2$ [M + 1]$^+$: 312.0830; found: 312.0843.

3. Results and Discussion

The T3P®-mediated model reaction of 2-naphthol (**1**), methyl carbamate (**2**), and 3-fluorobenzaldehyde (**3**) (1 equiv. of each) was optimized by varying different experimental parameters (Scheme 2, Table 1). Initially, the effect of the reaction time and the molar excess of the components were investigated. Based on preliminary experiments, the reaction was performed in ethyl acetate (EtOAc) at room temperature for 26 h using 1 equiv. of T3P® (Table 1, entry 1), resulting in the desired racemic product (**4a**) in 32% yield. The progress of the reactions was followed by TLC and HPLC-MS. Next, the temperature was raised to 77 °C. It was found that 2 h of reaction time in EtOAc under reflux is sufficient for full conversion, and the yield increased to 53% (Table 1, entry 2). In the absence of T3P®, the product (**4a**) was not detected

(Table 1, entry 3). At the next stage of the optimization, the amount of the reactants was screened. Adding methyl carbamate (**2**), 3-fluorobenzaldehyde (**3**), and T3P® in 1.1 equiv. or 1.3 equiv. excess to 2-naphthol (Table 1, entries 4,5), the yield increased to 83% for both reactions that might be explained with the mode of action of T3P®, i.e., sometimes, it can react not only in the cyclic, but also in the open-chain form after the addition of one water molecule multiplying the activity [33]. In the case of applying 1.5 equiv. and 5.0 equiv. T3P®, a slight decrease in the yields was observed with the higher amount of the additive (81% and 73%, respectively) (Table 1, entries 6,7) possibly due to degradation. The last reaction was refluxed for 5 h, suggesting that the larger amount of the dehydrating agent and the longer reaction time do not influence the reaction further. After the amount of the components was optimized, the proper solvent of the reaction was screened for. The products were obtained in high yields (73–91%, Table 1, entries 8–14) in each case, but an outstanding result of 91% suggested the use of toluene as the most appropriate solvent (Table 1, entry 13). Moreover, it was found that the reaction time could be decreased to 30 min without significant decrease in the yield (Table 1, entry 14).
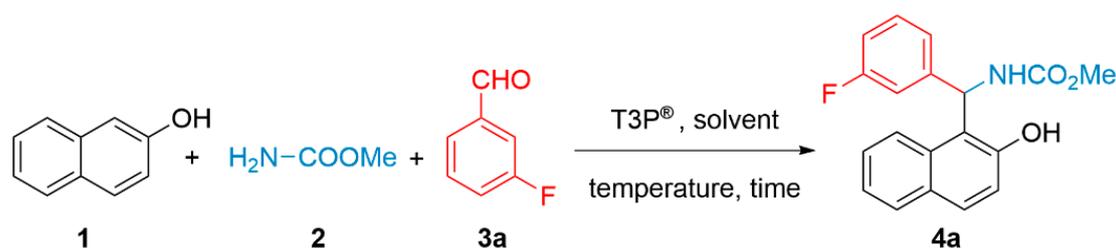
Scheme 2. The components of the optimized Betti reaction.

Table 1. Optimization of the Betti reaction **1** + **2** + **3a**→**4a**. The best conditions are highlighted by bolding.

Entry	1/2/3a	T3P® (equiv.)	Time (h)	Solvent	Temperature (°C)	Yield (%)
1	1/1/1	1	26	EtOAc	r.t.	32
2	1/1/1	1	2	EtOAc	77	53
3	1/1/1	0	2	EtOAc	77	0
4	1/1.1/1.1	1.1	2	EtOAc	77	83
5	1/1.3/1.3	1.3	2	EtOAc	77	83
6	1/1.1/1.1	1.5	2	EtOAc	77	81
7	1/1.1/1.1	5	5	EtOAc	77	73
8	1/1.1/1.1	1.1	2	THF	66	90
9	1/1.1/1.1	1.1	2	MeCN	82	73
10	1/1.1/1.1	1.1	2	CHCl$_3$	62	89
11	1/1.1/1.1	1.1	2	MTBE	65	83
12	1/1.1/1.1	1.1	2	MeTHF	80	85
13	**1/1.1/1.1**	**1.1**	**2**	**PhMe**	**80**	**91**
14	**1/1.1/1.1**	**1.1**	**0.5**	**PhMe**	**80**	**89**

With the optimized reaction conditions in hand, the scope and limitations of the T3P®-assisted synthesis of 1-carbamatoalkyl 2-naphthols (**4**) were examined. The reaction of 2-naphthol (**1**) and methyl carbamate (**2**) with various aromatic aldehydes (**3a–i**) was studied in toluene at 80 °C for 30 min (Scheme 3). The products **4a–i** were obtained in good to high yields (60–90%). Aromatic aldehydes containing electron-withdrawing groups (EWG, e.g., chlorine and/or bromine) were compatible with the reaction, providing **4a**, **4c**, and **4f** in 71–89% yields. However, the phenoxy derivatives (**4b** and **4e**) were isolated in different, 60% and 90% yields, respectively. The position of the electron-donating phenoxy group seemed to be limiting the efficacy; particularly, in the para position, it strongly hindered the reaction (**4b**, 60% yield) possibly by slowing the formation and weakening the reactivity of the electrophilic imine intermediate. Heteroaromatic aldehydes (**3g–i**) provided good yields (**4g–i**, 66–77%).

The application of benzaldehyde (**3d**) gave product **4d** in 81% yield after 30 min. When the reaction mixture forming **4d** was heated under microwave (MW) conditions, the corresponding product (**4d**) was obtained in 76% yield after 15 min, suggesting that the MW has some rate-enhancing effect for the reaction. To the best of our knowledge, naphthol derivatives **4a,c,d,e,f,h** are new compounds with no precedence in the scientific literature.
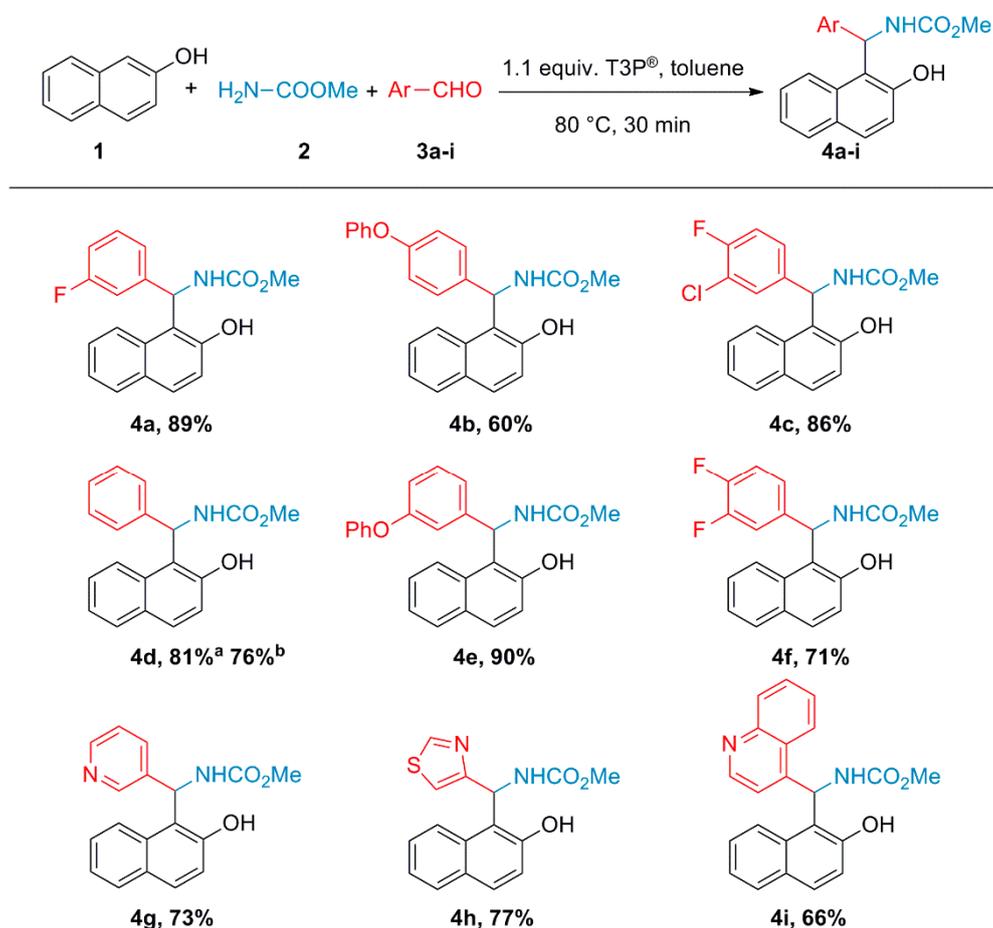
Scheme 3. Scope and limitations for the Betti reaction with propylphosphonic anhydride (T3P®) for the synthesis of 1-carbamatoalkyl 2-naphthols. [a] 80 °C, 30 min; [b] microwave (MW), 80 °C, 15 min.

In some cases, more by-products could be detected by HPLC-MS. The side products were isolated, and the structures were elucidated by NMR spectroscopy. It was found that the side product is a naphta[1,2]oxazinone derivative resulting from the intramolecular ring closure of compounds **4**. Based on this finding, the reaction conditions for the cyclization were optimized starting from **4d** (Scheme 4, Table 2). Executing the reaction at lower temperatures did not result in the desired product even after longer reaction times (Table 2, entries 1–4). After raising the excess of T3P® to 2 equiv. and elevating the temperature to 160 °C, the naphthoxazinone could be isolated in 75% yield after 1 h (Table 2, entry 5). Using a lower quantity of T3P® did not lead to full conversion (Table 2, entry 6), while in a larger excess, the formation of unidentified decomposition products was observed with a significant decrease in the yield (Table 2, entry 7). Heating the reaction mixture under microwave (MW) conditions caused decomposition similarly, and **5d** could be isolated only in low yields (Table 2, entries 8,9).
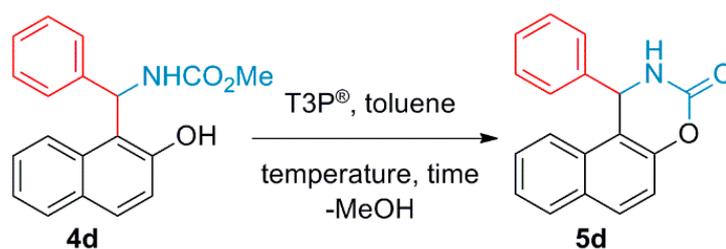
Scheme 4. The cyclization used for the optimization procedure.

Table 2. Optimization of the conditions for the reaction **4d→5d.** The best conditions are highlighted by bolding.

Entry	T3P® (equiv.)	Temperature (°C)	Reaction Time	Yield (%)
1	-	80	26 h	n.r. [a]
2	1.1	80	30 min	0 [b]
3	1.1	135	4 h	0 [b]
4	2	135	70 min	0 [b]
5	**2**	**160**	**60 min**	**75**
6	1.1	160	90 min	47
7	3	160	45 min	50
8	2	135 [c]	90 min	18
9	2	160 [c]	30 min	36

[a] n.r. = No reaction. [b] Only traces of product could be detected by HPLC-MS. [c] The reaction mixture was heated under microwave (MW) conditions.

After the optimization of the two separate reactions, we aimed to develop a one-pot protocol for the synthesis of naphta[1,2-*e*]oxazinone derivatives. It should be noted that the two separate steps with double work-up and purification resulted in 81% × 75% = 61% (Δ) and 75% × 75% = 56% (MW) total yields for the model compound **5d**. Thus, we challenged to reach at least similar efficacy. Three different synthesis pathways were elaborated to find the efficient method, performed with conventional heating in a sealed tube (**A**–**C**) and under MW conditions (**D**–**F**), as well (Scheme 5, Table 3). First, we have challenged the one-pot procedure by applying 2-naphthol (**1**), methyl carbamate (**2**) (1.1 equiv.), benzaldehyde (**3d**) (1.1 equiv.), and T3P® (3.1 equiv.) and heating the reaction at 160 °C for 90 min in toluene (Scheme 5 **A**,**D**). The conventional heating (**A**) resulted in a yield of 26%, while on the contrary, in the MW procedure, (**D**) **5d** was obtained in 38%. This result led us to the conclusion that the two reaction steps should be treated differently, either by increasing the reaction temperature sequentially (**B** and **E**), or together with that by adding the T3P® reagent in two portions (**C** and **F**). In pathway **B** and **E**, all the necessary T3P® was added at the beginning of the reaction, and the reaction times and temperatures were taken from the separately optimized steps. First, the temperature was held at 80 °C for the first step (30 min at **B1** and 15 min at **E1**), and then raised to 160 °C for the ring closure (90 min at **B2** and 35 min at **E2**). Naphthoxazinone **5d** was isolated in 28% in the conventional way (**B**), while in this case, the MW conditions (**E**) led to 52% yield. The most complicated pathways **C** and **F** resulted in moderate to good yields. If the T3P® was added in two portions (1.1 equiv. at 80 °C and 2.0 equiv. at 160 °C), the expected product **5d** was formed in 51% yield under conventional heating (**C**) and in 45% yield under MW conditions (**F**). It should be noted that there was no significant remaining starting material in any cases, but different amounts of small degradation products were detected in the HPLC-MS. In summary, pathway **E** was found to be the most efficient for the one-pot synthesis of **5d** from 2-naphthol (**1**), methyl carbamate (**2**), and benzaldehyde (**3d**). Although the total yield is lower than those for the two separate reactions, the total work time and costs for the reactions have been reduced, as only one work-up and purification procedure is required.

Table 3. One-pot ring-closing synthesis pathways (**A–F**) and optimization leading to naphtha[1,2-*e*]oxazinone **5d.** The best conditions are highlighted by bolding.

Method	Number of Steps	Reaction Time (min)		Temperature (°C)		T3P® (equiv.)		Yield (%)
MW/Δ	1 or 2	Step1	Step2	Step1	Step2	Step1	Step2	
A	Δ	1	90	-	160	-	3.1	-	26
B	Δ	2	30	90	80	160	3.1	-	28
C	Δ	2	30	90	80	160	1.1	2.0	51
D	MW	1	55	-	160	-	3.1	-	38
E	**MW**	**2**	**15**	**35**	**80**	**160**	**3.1**	**-**	**52**
F	MW	2	15	35	80	160	1.1	2.0	45
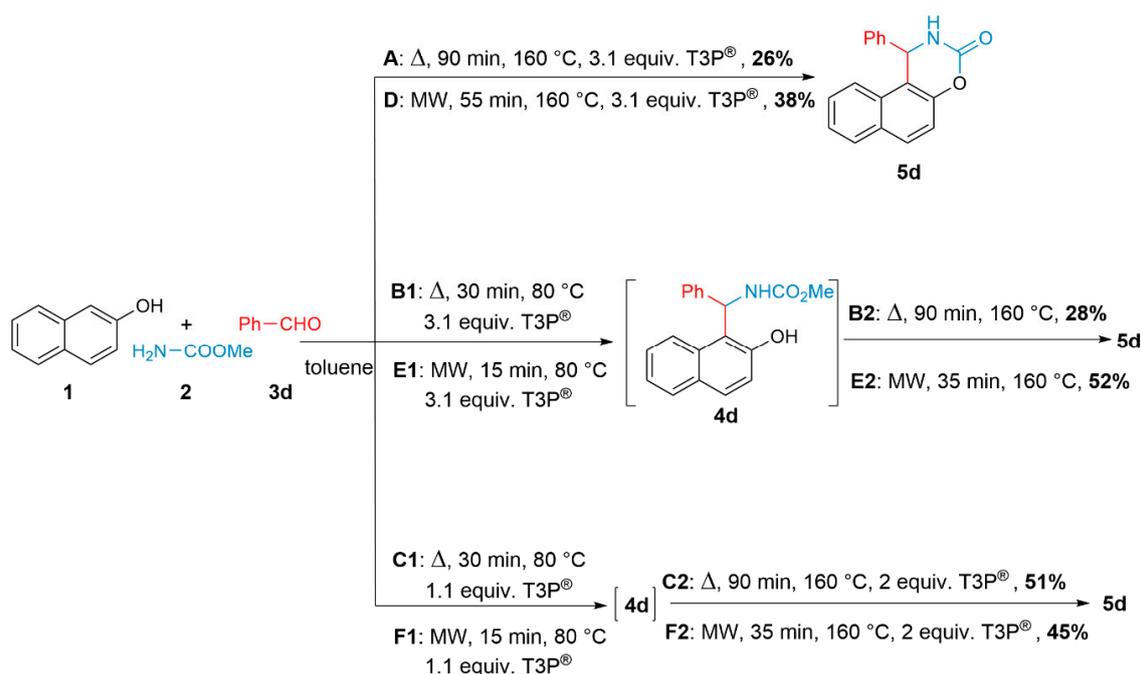
Scheme 5. One-pot reaction pathways (A–F) to the synthesis of naphta[1,2-*e*]oxazinone 5d.

After finding the suitable method for the T3P®-assisted one-pot synthesis of naphthoxazinones, the scope and limitations of the reaction were examined with aldehydes **3a–i** (Scheme 6).

The reactions with aldehydes **3a,c,e,f** went smoothly, resulting in moderate yields (41–53%) similarly to benzaldehyde **3a**. Aldehyde **3b** equipped with the phenoxy group in the para position gave product **5b** in a low yield (23%), supposedly due to the weak efficacy observed earlier for the first step. Notably, in the case of the heterocyclic aldehydes, we were able to isolate a side product (**6g–i**) in very poor yield and observe unidentified decomposition products. The desired **5g–i** could only be detected by HPLC-MS. The side product has been identified as the adduct of T3P® to the Betti-product (Figure 1).

To the best of our knowledge, the four synthesized oxazinones **5b,c,e,f** have not been precedented in the scientific literature yet. The new derivatives have been characterized by ¹H and ¹³C-NMR, HRMS, and melting point (see Supplementary Material).
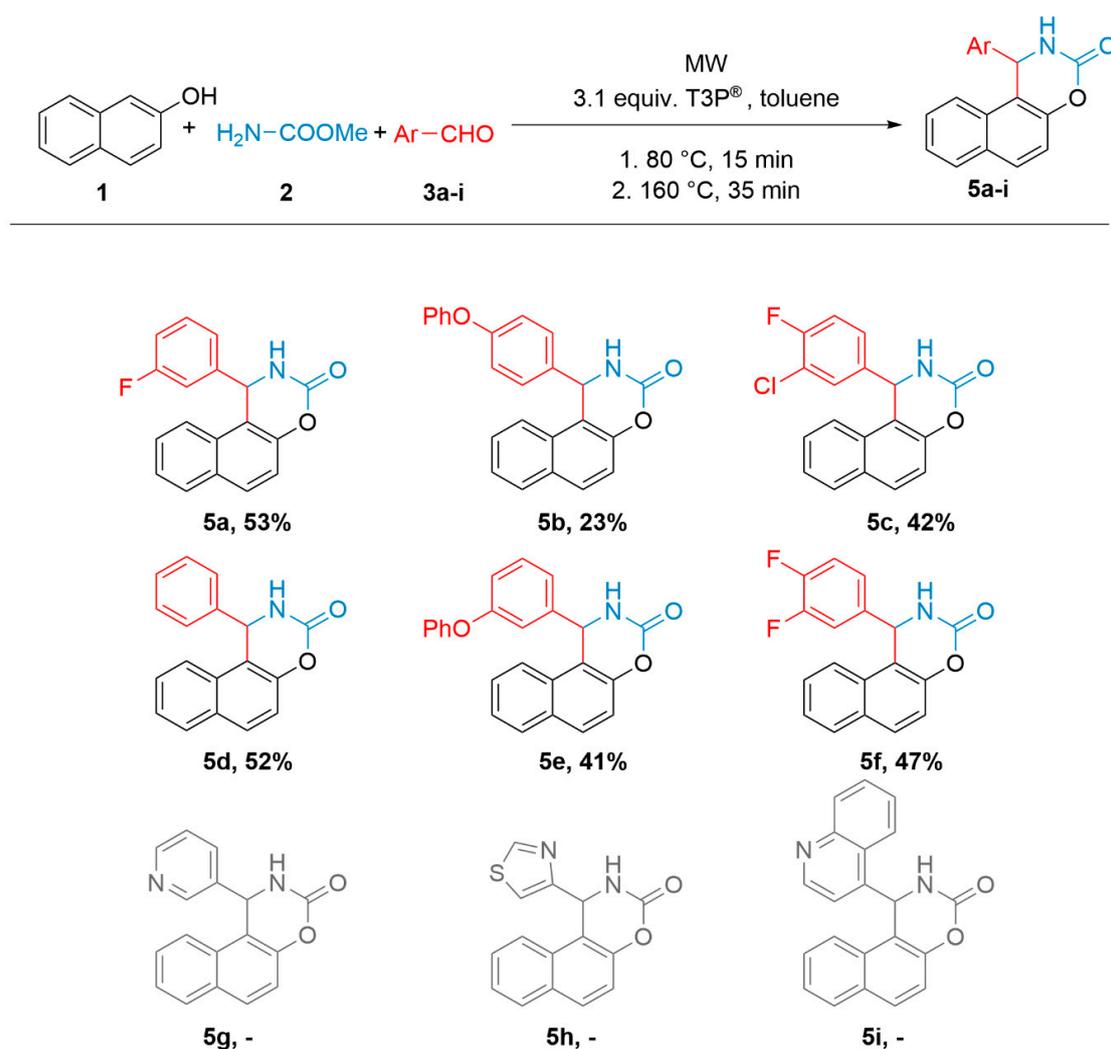
Scheme 6. Scope and limitations for the ring-closing reaction with T3P® for the synthesis of naphta[1,2-*e*]oxazinone derivatives.
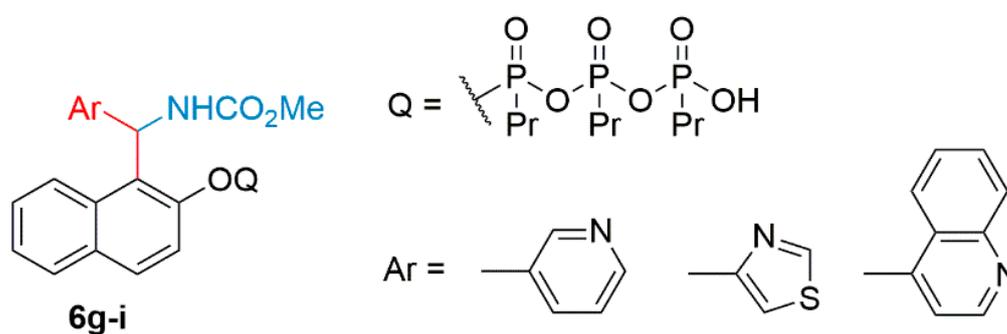
Figure 1. The identified side products in the one-pot procedure derived from **4g–i**.

A plausible mechanism for the formation of carbamates **4** via the Betti reaction in the presence of T3P® and the T3P®-mediated synthesis of naphtha[1,2-*e*]oxazinones (**5**) is outlined in Scheme 7 **A** and **B**, respectively. The first step is the T3P®-promoted condensation of aldehyde **3** and methyl carbamate (**2**), forming an imine-type intermediate (**7**) along with 1,5-dihydroxy-1,3,5-tripropyltriphosphoxane 1,3,5-trioxide (T3P® + H$_2$O abbreviated as QOH, **8**). In the next step, the nitrogen atom of the C=N bond is protonated, and the iminium ion (**9**) reacts with naphthalen-2-olate (**10**) in a nucleophilic addition, forming 2-oxo-1,2-dihydronaphtalen-1-yl intermediate **11**. Finally, the aromatic system is

stabilized again by a proton exchange leading to **4**. The cyclization-forming heterocycle **5** presumably begins with the deprotonation of the 1-carbamatoalkyl naphthol derivative **4**. This is followed by the nucleophilic addition of the anion to the carbonyl group and the subsequent MeOH elimination, resulting in the tricyclic product **5**. From the proposed intermediates, imine **7** and Betti-product **4** could be detected by HPLC-MS.
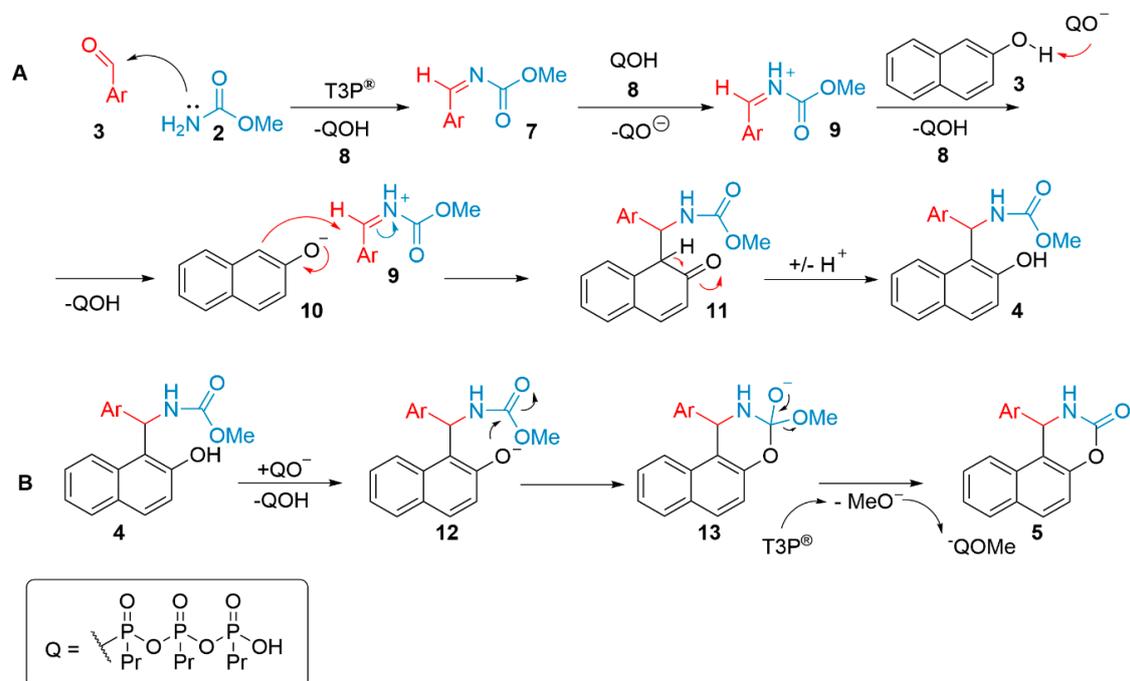
Scheme 7. Proposed mechanism for the T3P®-promoted formation of **4** (**A**) and the T3P®-promoted ring-closing reaction to naphtha[1,2-*e*]oxazinone **5** (**B**).

4. Conclusions

A three-component reaction has been optimized between 2-naphthol, methyl carbamate, and aromatic aldehydes in the presence of the dehydrating additive T3P®. The formed 1-carbamatoalkyl 2-naphthols have been transformed, further leading to naphthoxazinones. The successful multicomponent reaction and the subsequent ring closure have been optimized in a one-pot manner, resulting in a three-component sequential multistep cascade.

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