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 TiO2–HClO4 [18], magnesium hydrogen sulphate [19], silica perchloric acid [20], trityl chloride [21], silica-supported sodium hydrogen sulphate [22], and P2O5 supported on SiO2 [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].

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.

Scheme 1. Schematic illustration of the Betti-type three-component reaction of 2-naphthol, methyl carbamate, and 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. 1H NMR and 13C NMR spectra were recorded at 303 K on a Bruker Avance III HD (600 and 150 MHz for 1H and 13C NMR spectra, respectively, a Bruker Avance III (400 and 100 MHz for 1H and 13C NMR spectra, respectively) (Billerica, MA, USA), or a Varian Unity Inova 300 MHz spectrometer (300 and 75 MHz for 1H and 13C NMR spectra, respectively) (Oxford, UK). DMSO-d6 and/or CDCl3 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 1H and 13C 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 NaHCO3. The organic phase was separated, dried (MgSO4), 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). 1H NMR (600 MHz, DMSO-d6) 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, CH3) ppm. 13C NMR (150 MHz, DMSO-d6) 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
Methyl ((2-hydroxynaphthalen-1-yl)(3-chloro-4-fluorophenyl)methyl)carbamate (4a). Yield: 249 mg, (81%); white crystals; mp. 207–210 °C, (Lit.: 207–209 °C) [8]. 1H NMR (600 MHz, DMSO-d6) δ 10.21 (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, CH3) ppm. 13C NMR (150 MHz, DMSO-d6) δ 157.2 (C=), 159.4 (C=), 149.3 (C=), 140.5 (C=), 132.0 (C=), 129.8 (C=), 128.8 (C=), 128.5 (C=), 121.7 (C=), 119.0 (C=), 118.8 (C=), 118.7 (C=), 117.1 (C=), 116.8 (C=), 52.1 (CH3), 50.6 (CH). HRMS calcd. for C19H14NO3 [M+H]+: 324.0947; found: 324.0920.

Methyl ((2-hydroxynaphthalen-1-yl)(3,4-difluorophenyl)methyl)carbamate (4b). Yield: 225 mg, (73%); white crystals; mp. 207–210 °C, (Lit.: 207–209 °C) [8]. 1H NMR (600 MHz, DMSO-d6) δ 10.21 (s, 1H, OH), 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, CH3) ppm. 13C NMR (150 MHz, DMSO-d6) δ 156.8 (C=), 153.2 (C=), 147.8 (C=), 140.4 (C=), 134.0 (C=), 132.0 (C=), 129.9 (C=), 128.8 (C=), 128.5 (C=), 126.9 (C=), 123.4 (C=), 122.9 (C=), 122.8 (C=), 118.6 (C=), 118.1 (C=), 51.9 (CH3), 48.9 (CH) ppm. HRMS calcd. for C19H16NO3 [M+H]+: 307.1233; found: 307.1231.
Methyl ((2-hydroxynaphthalen-1-yl)(thiazol-4-yl)methyl)carbamate (4h). Yield: 242 mg (77%); white crystals; mp. 208–210 °C. 1H NMR (600 MHz, DMSO-d6) 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. 13C NMR (150 MHz, DMSO-d6) δ 158.0 (C=), 156.4 (=CO), 153.8 (=CH), 153.1 (C=), 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 (CH3), 48.9 (CH) ppm. HRMS calcd. for C16H15N2O3S [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. 1H NMR (600 MHz, DMSO-d6) 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, CH3) ppm. 13C NMR (150 MHz, DMSO-d6) δ 162.5 (C=), 156.7 (C=), 153.5 (=CO), 150.3 (=CH), 148.1 (=CH), 141.8 (=CH), 132.7 (C=), 130.2 (=CH), 130.0 (=CH), 129.1 (=CH), 128.7 (=CH), 126.9 (C=), 126.6 (C=), 126.3 (C=), 123.6 (=CH), 123.0 (=C), 122.8 (=CH), 120.0 (=CH), 118.7 (=CH), 117.1 (=CH), 51.9 (CH3), 48.8 (CH) ppm. HRMS calcd. for C22H19N2O3 [M + H]+: 359.1390; found: 359.1396.

2.3. Ring-Closing Reaction from methyl ((2-hydroxynaphthalen-1-yl)(phenyl)methyl)carbamate (4d) to naphtha[1,2-e]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 NaHCO3 were added, and the organic phase was separated, dried (MgSO4), 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 naphtha[1,2-e]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 naphtha[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, 0.78 mL, (1.30 mmol, 2.0 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 NaHCO3, and the organic phase was separated, dried (MgSO4), filtered, evaporated to silica, and purified by flash column chromatography with hexane–ethyl acetate. 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-Pr2O), (Lit.: 218–220 °C) [35]. 1H NMR (300 MHz, DMSO-d6) δ 8.94 (m, 1H, NH), 8.01–7.10 (m, 10 H, Ar-H), 6.27 (m, 1H, CH) ppm. 13C NMR (75 MHz, DMSO-d6) 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), 115.7 (=C), 114.5 (C=), 114.1 (=CH), 53.8 (CH) ppm. HRMS calcd. for C18H13NO2F [M + H]+: 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-Pr2O). 1H NMR (300 MHz, CDCl3) δ 7.87–7.84 (m, 2H, Ar-H, NH), 7.55–6.94 (m, 14H, Ar-H), 6.08 (s, 1H, CH) ppm. 13C NMR (75 MHz, CDCl3) 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_2O). ¹H 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. ¹³C 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_2FCl [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_2O), (Lit.: 218– 220 °C) [36]. ¹H 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; ¹³C 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), 129.3 (=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_2O). ¹H 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; ¹³C 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_2O). ¹H 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. ¹³C 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), 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_2F_2 [M + H]^+: 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 $1 + 2 + 3a \rightarrow 4a$. The best conditions are highlighted by bolding. |
|---|---|---|---|---|---|---|
| Entry | 1/2/3a | T3P$^\oplus$ (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 | 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$^\oplus$-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 naptha[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 naphtha[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.
Scheme 5. One-pot reaction pathways (A–F) to the synthesis of naphtha[1,2-e]oxazinone 5d.

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/∆            | Step1   | Step2   | Step1 | Step2 | Step1 | Step2 |
| A      | ∆ 1             | 90      | -       | 160   | -     | 3.1   | -     | 26    |
| B      | ∆ 2             | 30      | 90      | 80    | 160   | 3.1   | -     | 28    |
| C      | ∆ 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    |

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).

Figure 1. The identified side products in the one-pot procedure derived from 4g–i.
To the best of our knowledge, the four synthesized oxazinones \(5_{b,c,e,f}\) have not been precedent in the scientific literature yet. The new derivatives have been characterized by \(^1\)H and \(^{13}\)C-NMR, HRMS, and melting point (see Supplementary Material).

A plausible mechanism for the formation of carbamates \(4\) via the Betti reaction in the presence of T\(3\)P\(^{\circ}\) and the T\(3\)P\(^{\circ}\)-mediated synthesis of naphtha[1,2-c]oxazinones \(5\) is outlined in Scheme 7 A and B, respectively. The first step is the T\(3\)P\(^{\circ}\)-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 (T\(3\)P\(^{\circ}\) + 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-dihyronaphtalen-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 T\(3\)P\(^{\circ}\)-promoted formation of 4 (A) and the T\(3\)P\(^{\circ}\)-promoted ring-closing reaction to naphtha[1,2-c]oxazinone 5 (B).](image)

4. Conclusions

A three-component reaction has been optimized between 2-naphthol, methyl carbamate, and aromatic aldehydes in the presence of the dehydrating additive T\(3\)P\(^{\circ}\). 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.

Supplementary Materials: The following are available online at www.mdpi.com/2227-9093/3/3/s1. \(^1\)H and \(^{13}\)C NMR spectra of the synthesized compounds.

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References

1. Ruijter, E.; Scheffelaar, R.; Orru, R.V.A. Multicomponent Reaction Design in the Quest for Molecular Complexity and Diversity. Angew. Chem. Int. Ed. 2011, 50, 6234–6246.
2. Slobbe, P.; Ruijter, E.; Orru, R.V.A. Recent applications of multicomponent reactions in medicinal chemistry. Med. Chem. Commun. 2012, 3, 1189–1218.
3. Afshari, R.; Shaabani, A. Materials Functionalization with Multicomponent Reactions: State of the Art. ACS Comb. Sci. 2018, 20, 499–528.

Wang, M.; Liu, Y.; Song, Z.; Zhao, S. A convenient three-component synthesis of carbamatoalkyl naphthols catalyzed by cerium ammonium nitrate. Bull. Chem. Soc. Ethiop. 2013, 27, 421–426.

5. Zare, A.; Akbarzadeh, S.; Foroozani, E.; Kaveh, H.; Moosavi-Zare, A.R.; Hasaninejad, A.; Mokhlesi, M.H.; Zolfigol, M.A. Triethylamine-bonded sulfonic acid ([Et3N–SO3H]Cl): A highly efficient and homogeneous catalyst for the condensation of 2-naphthol with arylaldehydes and amides (alkyl carbamates or thioamides). J. Sulfur Chem. 2012, 33, 259–272.

6. Zare, A.; Merajoddin, M.; Moosavi-Zare, A.R.; Zarei, M.; Beyzavi, M.H.; Zolfigol, M.A. Design and characterization of nano-silica-bonded 3-n-propyl-1-sulfonic acid imidazolium chloride (nano-SB-[PSIM][Cl]) as a novel, heterogeneous and reusable catalyst for the condensation of arylaldehydes with β-naphthol and alkyl carbamates. Res. Chem. Intermed. 2016, 42, 2365–2378.

7. Dadhania, H.N.; Raval, D.K.; Dadhania, A.N. Magnetically retrievable magnetite (Fe3O4) immobilized ionic liquid: An efficient catalyst for the preparation of 1-carbamatoalkyl-2-naphthols. Catal. Sci. Technol. 2015, 5, 4806–4812.

8. Dehghan, M.; Davoodnia, A.; Bozorgmehr, M.R.; Bamoharram, F.F. Evaluation of catalytic activity of two newly prepared functionalized sulfonic acids ionic liquids in the synthesis of carbamatoalkyl naphthols under mild conditions. Russ. J. Gen. Chem. 2017, 87, 311–318.

9. Tavakoli-Hoseini, N.; Heravi, M.M.; Bamoharram, F.F.; Davoodnia, A. Brønsted acidic ionic liquids as efficient catalysts for clean synthesis of carbamatoalkyl naphthols. Bull. Korean Chem. Soc. 2011, 32, 787–792.

10. Dabiri, M.; Delbari, A.S.; Bazgir, A. A Simple and Environmentally Benign Method for the Synthesis of Naphthoxazin-3-one Derivatives. Heterocycles 2007, 71, 543–548.

11. Patel, N.; Katheriya, D.; Dadhania, H.; Dadhania, A. Graphene oxide supported dicationic ionic liquid: An efficient catalyst for the synthesis of 1-carbamatoalkyl-2-naphthols. Res. Chem. Intermed. 2019, 45, 5595–5607.

12. Kundu, D.; Majee, A.; Hajra, A. Zwitterionic-type molten salt: An efficient mild organocatalyst for synthesis of 2-amidoalkyl and 2-carbamatoalkyl naphthols. Catal. Commun. 2010, 11, 1157–1159.

13. Shaﬁee, M.R.M.; Molondi, R.; Ghashang, M. Preparation of Methyl (2-hydroxynaphthalen-1-yl)(aryl)methylcarbamate derivatives using magnesium (II) 2,2,2-trifluoroacetate as an efficient catalyst. J. Chem. Res. 2011, 35, 622–625.

14. Yang, J.-M.; Jiang, C.-N.; Dong, H.; Fang, D. Synthesis of 1-carbamatoalkyl-2-naphthols in Tween® 20 Aqueous Micelles, J. Chem. Res. 2013, 37, 279–281.

15. Yarahmadi, H.; Shazerian, R. Sulfamic acid Functionalised Magnetic Nanoparticles: An Efficient Solid Acid for the Multicomponent Condensations. J. Chem. Res. 2012, 36, 52–55.

16. Wang, M.; Wang, Q.L.; Zhao, S.; Wan, X. Solvent-free one-pot synthesis of 1-carbamatoalkyl-2-naphthols by a tin tetrachloride catalyzed multicomponent reaction. Monatsh. Chem. 2013, 144, 975–980.

17. Zare, A.; Kaveh, H.; Merajoddin, M.; Moosavi-Zare, A.R.; Hasaninejad, A.; Zolfigol, M.A. Saccharin Sulfonic Acid (SASA) as a Highly Efficient Catalyst for the Condensation of 2-Naphthol With Arylaldehydes and Amides (Thioamides or Alkyl Carbamates) Under Green, Mild, and Solvent-Free Conditions. J. Sulfur Chem. 2013, 188, 573–584.

18. Shaterian, H.R.; Mohammadnia, M. Nanocrystalline TiO2–HClO4 catalyzed three-component preparation of derivatives of 1-amidoalkyl-2-naphthol, 1-carbamato-alkyl-2-naphthol, 1-(α-carboxyalkyl)-2-naphthol, and 12-aryl-8,9,10,12-tetrahydrobenzo[α]-xanthene-11-one. Res. Chem. Intermed. 2013, 39, 4221–4237.

19. Ghashang, M. Preparation of methyl/benzyl(2-hydroxynaphthalen-1-yl)(aryl)methylcarbamate derivatives using magnesium hydrogen sulfate. Res. Chem. Intermed. 2014, 40, 1357–1364.

20. Shaterian, H.R.; Hosseiniyan, A.; Ghashang, M. Synthesis of New and Novel N-Protected 1-Aminoalkyl-2-naphthol Derivatives. Synth. Commun. 2009, 39, 2560–2574.
21. Khazaei, A.; Zolfigol, M.A.; Moosavi-Zare, A.R.; Abi, F.; Zare, A.; Kaveh, H.; Khakyzadeh, V.; Kazem-Rostami, M.; Parhami, A.; Torabi-Monfared, H. Discovery of an in situ carbocationic system using trityl chloride as a homogeneous organocatalyst for the solvent-free condensation of β-naphthol with aldehydes and amides/thioamides/alkyl carbamates in neutral media. *Tetrahedron* 2013, 69, 212–218.

22. Shaterian, H.R.; Hosseinian, A.; Ghashang, M. A three-component novel synthesis of 1-carbamato-alkyl-2-naphthol derivatives. *Tetrahedron Lett.* 2008, 49, 5804–5806.

23. Ghasemi, A.; Davoodnia, A.; Pordel, M.; Tavakoli-Hoseini, N. P:O supported on SiO2 as an efficient and reusable catalyst for rapid one-pot synthesis of carbamatoalkyl naphthols under solvent-free conditions. *Cogent Chem.* 2017, 3, 1317582.

24. Shen, A.Y.; Tsai, C.T.; Chen, C.L. Synthesis and cardiovascular evaluation of N-substituted 1-aminomethyl-2-naphthols. *Eur. J. Med. Chem.* 1999, 34, 877–882.

25. Latif, N.; Mishriky, N.; Assad, F.M. Carbonyl and thiocarbonyl compounds. XIX. Intramolecular cyclization of (2-nitroethylene)aryl N-arylcarbamates: Synthesis of newer series of 3,4-dihydro-2H-1,3-oxazin-2-ones and their antimicrobial activities. *Aust. J. Chem.* 1982, 35, 1037–1043.

26. Wissmann, H.; Kleiner, H.-J. New Peptide Synthesis. *Angew. Chem. Int. Ed.* 1980, 19, 133–134.

27. Basavarajbhu; Vishwanatha, T.M.; Panguluri, N.R.; Sureshbabu, V.V. Propanephesphonic Acid Anhydride (T3P®) - A Benign Reagent for Diverse Applications Inclusive of Large-Scale Synthesis. *Synthesis* 2013, 45, 1569–1601.

28. Waghmare, A.A.; Hinduapur, R.M.; Pati, H.N. Propylphosphonic anhydride (T3P®): An expedient reagent for organic synthesis. *Rev. J. Chem.* 2014, 4, 53–131.

29. Henyecz, R.; Milen, M.; Kánaí, K.; Keglevich, G. *Organophosphorus Chemistry: Novel Developments*; De Gruyter: Berlin, Germany, 2018.

30. Milen, M.; Ábrányi-Balogh, P.; Dancsó, A.; Frigyes, D.; Pongó, L.; Keglevich, G. T3P®-promoted Kabachnik-Fields reaction: An efficient synthesis of α-aminophosphonates. *Tetrahedron Lett.* 2013, 54, 5430–5433.

31. Milen, M.; Dancsó, A.; Földesi, T.; Slégel, P.; Volk, B. Propylphosphonic anhydride (T3P®) mediated one-pot three-component synthesis of racemic dialkyl (2-substituted-3-oxo-2,3-dihydro-1H-isooindol-1-yl)phosphonates. *Tetrahedron* 2016, 72, 5091–5099.

32. Milen, M.; Dancsó, A.; Földesi, T.; Volk, B. Study on the propylphosphonic anhydride (T3P®) mediated Ugi-type three-component reaction. Efficient synthesis of an α-amino amide library. *Tetrahedron* 2017, 73, 70–77.

33. Varga, V.; Milen, M.; Ábrányi-Balogh, P. Propylphosphonic anhydride (T3P®) mediated synthesis of 3-oxoisooindoline-1-carboxamides from 2-formylenzoic acid, amines, and isocyanides. Preparation of isoindolinelone alkaldoids. *Tetrahedron Lett.* 2018, 59, 3683–3689.

34. Ábrányi-Balogh, P.; Földesi, T.; Grün, A.; Volk, B.; Keglevich, G.; Milen, M. Synthetic study on the T3P®-promoted one-pot preparation of 1-substituted-3,4-dihydro-β-carbolines by the reaction of tryptamine with carboxylic acids. *Tetrahedron Lett.* 2016, 57, 1953–1957.

35. Rao, G.B.D.; Kaushik, M.P.; Halve, A.K. An efficient synthesis of naphtha[1,2-e]oxazine and 14-substituted-14H-dibenzo[a,j]xanthene derivatives promoted by zinc oxide nanoparticle under thermal and solvent-free conditions. *Tetrahedron Lett.* 2012, 53, 2741–2744.

36. Dabiri, M.; Delbari, A.S.; Bazgir, A. A Novel Three-Component, One-Pot Synthesis of 1,2-Dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one Derivatives under Microwave-Assisted and Thermal Solvent-Free Conditions. *Synlett* 2007, 5, 821–823.