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Use of triphenylphosphine-bromotrichloromethane (PPh₃-BrCCl₃) in the preparation of acylhydrazines, *N*-methylamides, anilides and *N*-arylmaleimides from carboxylic acids

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Abstract: In certain countries, many of the reagents used to transform carboxylic acids to acyl halides such as phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride, phosphoryl chloride, thionyl chloride and sulfuryl chloride are difficult to come by. Against this background, the authors developed the reaction system triphenylphosphine (PPh₃) – bromotrichloromethane (BrCCl₃) to prepare acyl halides *in situ*. In the following, the use of this reagent combination is joined with the reaction of the *in situ* prepared acyl halides with nitrogen nucleophiles, specifically with hydrazines, methylamine and anilines. The reaction is also used in an intramolecular variant by the reaction of maleianilic acids to *N*-arylmaleimides..

Keywords: Appel-type reaction; *N*-arylmaleimides, acylhydrazines, anilides

1. Introduction

Although there are a number of ways to transform carboxylic acids to acyl halides, the reagents needed such as phosphorus trichloride, phosphorus tribromide, phosphorus pentachloride, phosphoryl chloride, thionyl chloride and sulfuryl chloride are not always available in certain countries. Against this background, the authors developed the reaction system triphenylphosphine (PPh₃) – bromotrichloromethane (BrCCl₃) to prepare acyl halides *in situ* [1,2]. This reaction system is a variation of the Appel reagent [3], where tetrachloromethane (CCl₄) is replaced by the environmentally less hazardous BrCCl₃. It was noted that the *in situ* prepared acyl halides could be reacted with alcohols, and primary and secondary amines to esters and amides, respectively [4]. In the following, the treatment of carboxylic acids is followed by their reaction with hydrazines, methylamine and anilines. Also, further examples [5] will be given to transform maleianilic acids to *N*-arylmaleimides with the action of PPh₃-BrCCl₃ in the presence of triethylamine as base.

2. Materials and Methods

3.1. General remarks

Melting points were measured on a Stuart SMP 10 melting point apparatus and are uncorrected. Infrared spectra were measured with a Thermo/Nicolet Nexus 470 FT-IR ESP spectrometer and a Perkin Elmer Spectrum Two spectrometer. ¹H and ¹³C NMR spectra were recorded with a Varian 400 NMR spectrometer (¹H at 395.7 MHz, ¹³C at 100.5 MHz). The assignments of the carbon signals were aided by DEPT 90 and DEPT 135 experiments (DEPT = Distortionless Enhancement by Polarisation Transfer). The chemical shifts are relative to TMS (solvent CDCl₃, unless otherwise noted). Mass

spectra were measured with a JMS-01-SG-2 spectrometer, and with an Agilent QTOF 6540 UHD. Column chromatography, where necessary, was performed on recycled silica gel (S, 0.063 mm – 0.1 mm, Riedel de Haen and Merck grade 9385).

3.2. Starting materials

Benzoic acid (**1a**), 4-nitrobenzoic acid (**1g**), 2,4-dichlorophenylacetic acid (**6c**) (Wako), methylammonium chloride (Merck-Schuchardt), cinnamic acid (**4a**) (Merck-Schuchardt), 4-methoxycinnamic acid (**4b**) (Fluka), 4-hydroxybenzoic acid (BDH Chemicals Ltd.), aniline (**2d**) (Aldrich), p-toluidin (**2b**) (4-methylaniline, Merck-Schuchardt), ammonium hydroxide (aq. solution of ammonia, 25 wt%, Sigma Aldrich), and 1-methyl-1-phenylhydrazine (Fluka) were acquired commercially. 3-Chlorobenzoic acid (**1b**), 4-bromobenzoic acid (**1f**), 3-bromobenzoic acid (**1d**), 2-bromobenzoic acid (**1c**), 2,3-dimethoxybenzoic acid (**1h**) and 4-methoxybenzoic acid (**1e**, anisidic acid) were prepared from the respective benzaldehydes by oxidation with AgO in basic medium. 4-Alkoxybenzoic acids were prepared in three steps from 4-hydroxybenzoic acid (transformation to the methyl ester with CH₃OH/H₂SO₄, alkylation of the phenolic function with KOH, Alkyl-I, DMSO [6] and hydrolysis with aq. NaOH in CH₃OH). 4-Ethoxy- and 4-propoxyaniline, **18a** and **18b**, were prepared from 4-hydroxyacetanilide by alkylation to the corresponding 4-alkoxyacetanilides **17a/17b** (KOH, Alkyl-I, DMSO [6]) with their subsequent hydrolysis (NaOH, dioxane-MeOH (5.5:1 v/v) [7]. 4-Triethylamine was distilled over solid KOH and subsequently stored over solid KOH. 2,4-Dinitrophenylhydrazine was dried before use in an oven at 37 °C for 48h.

3.2. General procedures

N-Methyl 3-chlorobenzamide (**9a**). – To a suspension of triphenylphosphine (PPh₃, 980 mg, 3.74 mol) in dry CH₂Cl₂ (12 mL), BrCCl₃ (760 mg, 3.83 mmol) is added dropwise. The solution which turns dark yellow is stirred at rt for 20 min. Then, 3-chlorobenzoic acid (**1b**, 485 mg, 3.10 mmol) is added, and the resulting mixture is heated at reflux for 25 min. Thereafter, methylammonium chloride (**8**, 360 mg, 5.41 mmol) is added, and subsequently dry triethylamine (940 mg, 9.30 mmol). The mixture is stirred at reflux for 5h. Thereafter, the cooled reaction mixture is subjected directly to column chromatography on silica gel (CH₂Cl₂-ether: 10:1) to give **9a** as a colorless solid (436 mg, 83%) (mp. 68 °C; Lit. 69-70 °C); IR (KBr/cm⁻¹) ν 3338, 3300, 3065, 1638, 1553, 1471, 1407, 1325, 743, 734, 678; ¹H NMR (400 MHz, DMSO-d₆) δ 2.75 (3H, s, NCH₃), 7.46 (1H, dd, ³J = 6.8 Hz, ³J = 6.4 Hz), 7.54 (1H, d, ³J = 6.8 Hz), 7.74 (1H, d, ³J = 6.4 Hz), 7.81 (1H, s), 8.58 (1H, bs, NH); ¹³C NMR (100.5 MHz, DMSO-d₆) δ 26.8 (NCH₃), 126.2 (CH), 127.3 (CH), 130.8 (CH), 131.4 (CH), 133.6 (C_{quat}), 136.8 (C_{quat}), 165.8 (C_{quat}, CO).

4-Nitrobenzoic acid *N*-methyl-*N*-phenyl hydrazide (**13d**). - To a suspension of triphenylphosphine (PPh₃, 980 mg, 3.74 mol) in dry CH₃CN (12 mL), BrCCl₃ (760 mg, 3.83 mmol) is added dropwise. The solution which turns dark yellow-brown is stirred at rt for 20 min. Then, 4-nitrobenzoic acid (**1g**, 525 mg, 3.14 mmol) is added and the mixture is stirred at 53 °C for 25 min. Thereafter, *N*-methyl-*N*-phenylhydrazine (**12**, 732 mg, 6.0 mmol) is added and the solution is stirred at 53 °C for 12h. The cooled mixture is concentrated to dryness *in vacuo*, and the residue is subjected to column chromatography on silica gel (CH₂Cl₂-ether 10:1) to give **13d** (665 mg, 78%) as a light yellow solid; IR (KBr/cm⁻¹) ν 3233, 1659, 1597, 1521, 1498, 1345, 1281, 850, 748, 691; ¹H NMR (400 MHz, DMSO-d₆) δ 3.17 (3H, s, CH₃), 6.74 (1H, t, ³J = 8.0 Hz), 6.81 (2H, d, ³J = 8.0 Hz), 7.20 (2H, dd, ³J = 8.0 Hz, ³J = 8.0 Hz), 8.09 (2H, d, ³J = 8.8 Hz), 8.32 (2H, d, ³J = 8.8 Hz), 10.93 (1H, s, NHCO); ¹³C NMR (100.5 MHz, DMSO-d₆) δ 40.5 (NCH₃), 112.9 (2C, CH), 119.1 (CH), 124.2 (2C, CH), 129.3[5] (2C, CH), 129.4 (2C, CH), 139.0 (C), 149.8 (C_{quat}), 150.0 (C_{quat}), 164.7 (C_{quat}, NCO).

N-4-Ethoxyphenylmaleimide (**21a**). - A solution of triphenylphosphine (1.89 g, 7.21 mmol) and bromotrichloromethane (BrCCl₃, 1.56 g, 7.86 mmol) in dry CH₃CN (20 mL) is stirred at rt for 30 min., during which it turns dark yellow. Then, maleanilic acid (**20a**) (1.35 g, 5.76 mmol) is added, and the

resulting mixture is stirred at 70°C for 40 min. Thereafter, dry triethylamine (750 mg, 7.42 mmol) is added dropwise over 15 min., and the resulting mixture is stirred at 70°C for 8h. The cooled mixture is added to water (50 mL), and the ensuing mixture is extracted with CH₂Cl₂ (3 X 35 mL). The combined organic phase is dried over anhydrous MgSO₄ and evaporated *in vacuo*. The residue is subjected to rapid column chromatography on silica gel (CH₂Cl₂) to give **21a** (1.0 g, 80%) a yellow, crystalline solid, mp. 134°C (Lit. 136-137°C [8]) IR (KBr/cm⁻¹) ν 3095, 2936, 2877, 1702, 1518, 1256, 720, 686; ¹H NMR (DMSO-d₆): δ 1.32 (3H, t, ³J = 6.7 Hz), 4.03 (2H, q, ³J = 6.7 Hz), 7.00 (2H, d, ³J = 8.6 Hz), 7.20 (2H, s), 7.40 (2H, d, ³J = 8.6 Hz).

Cinnamamide (11a). - A solution of triphenylphosphine (1.89 g, 7.21 mmol) and bromotrichloromethane (BrCCl₃, 1.56 g, 7.86 mmol) in dry CH₃CN (15 mL) is stirred at rt for 30 min., during which it turns dark yellow. Then, cinnamic acid (**4a**, 965 mg, 6.51 mmol) is added, and the resulting mixture is stirred at 70°C for 40 min. Thereafter, the solution is cooled to rt, and aq. ammonia (10 mL, ammonium hydroxide, 25 wt%) is added dropwise to the solution. Thereafter, the reaction mixture is heated at 70°C for 10h. The cooled solution is added to water (50 mL) and the ensuing mixture is extracted with CHCl₃ (2 X 30 mL). The combined organic phase is dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue is subjected to column chromatography over silica gel (CH₂Cl₂-ether 10:1) to give **11a** as a colorless solid (718 mg, 75%); mp. 148°C (Lit. 148-151 °C [9]); IR (KBr/cm⁻¹) ν 3371, 3165, 1660, 1607, 1492, 1449, 1397, 1245, 1114, 968, 862, 566, 526, 476; ¹H NMR (400 MHz, DMSO-d₆) δ 6.59 (1H, d, ³J = 15.6 Hz), 7.09 (1H, bs, NH), 7.36 – 7.41 (3H, m), 7.53 (2H, d, ³J = 6.8 Hz), 7.56 (1H, bs, NH); ¹³C NMR (100.5 MHz, DMSO-d₆) δ 122.6 (CH), 128.0 (2C, CH), 129.4 (2C, CH), 129.9 (CH), 135.2 (C_{quat}), 139.8 (CH), 167.3 (C_{quat}, CO).

4. Results and Discussion

Previously, it had been established that the reactions of the modified Appel reagent BrCCl₃-PPh₃ are similar to those of CCl₄-PPh₃. This includes the dehydration of aldoximes and amides to nitriles (1) and the amidation of carboxylic acids (4). Only the actual Appel reaction itself, i.e., the transformation of alkanols to haloalkanes with BrCCl₃-PPh₃ is more complex, where under certain conditions the transfer of the bromo-substituent vs. the chloro-substituent is not selective (2). In the following, the authors tried to examine whether amidation reactions of carboxylic acids with the less nucleophilic anilines would proceed equally well as with amines. Also, the authors investigated the reactions with hydrazines. Here, the use of ammonium salts such as methylammonium chloride and hydrazinium salts such as hydrazinium sulfate was probed as well as was the reaction of carboxylic acids with aq. ammonia in the presence of BrCCl₃-PPh₃. Finally, the scope of an intramolecular imidation was looked at to transform maleianilic acids to *N*-arylmaleimides (5)

The reaction of benzoic acids **1**, treated with BrCCl₃-PPh₃, with anilines **2** proceeded straightforward to give the anilides **3** (Table 1). The anilines were added slowly while the reaction mixture was at reflux. It was noted that the reactions are exothermic. The products were isolated by column chromatographic separation on silica gel. The reactions were also carried out successfully with cinnamic acids **4** (Table 2) and phenylacetic acids **6** (Table 3) as substrates.

The release of methylamine *in situ*, within a reaction mixture of initially carboxylic acid, triphenylphosphine and bromotrichloromethane by equilibration with added triethylamine was seen to work well, providing the corresponding *N*-methyl amides in acceptable yields (Table 4).

The reaction of aq. ammonia with the *in situ* prepared acyl halides proceeded equally well, showing that the amidation of the acyl halides proceeded faster than their hydrolysis (Tables 5 and 6).

For the reaction of the *in situ* prepared acyl halides, three available hydrazines/hydrazine salts available to us were chosen: 1-methyl-1-phenylhydrazine (**12**), 2,4-dinitrophenylhydrazine (**14**), and hydrazinium sulfate. 1-Methyl-1-phenylhydrazine is liquid, so its addition to the *in situ* prepared

acyl halides poses no problem. The 2,4-dinitrophenylhydrazine (**14**) commercially available to us was dampened with water, most likely to lessen the chance of a detonation of the material. Thus, hydrazine **14** was dried in an oven at 37 °C for 48h before use. Hydrazine itself was released in situ by equilibration of hydrazinium sulfate and triethylamine just as in the case of the use of methylammonium chloride (see above). In all cases, the reaction proceeded reasonably well, delivering acyl hydrazides **13** and **15** (Tables 7 and 8), and in the case of hydrazine itself, 1,2-bis(aryl)hydrazines **16** were obtained (Table 9).

Finally, our work (5) on using the modified Appel reagent $\text{PPh}_3\text{-BrCCl}_3$ for a ring closure of maleianic acids to *N*-maleimides was expanded slightly. While previously we had utilized anilines available to us commercially in these reactions, here, we prepared the anilines through a hydrolysis of the corresponding acetamides **17**. The general published procedure (7) works very well and allows for the construction of a substituted acetamide before releasing the substituted aniline by hydrolysis.

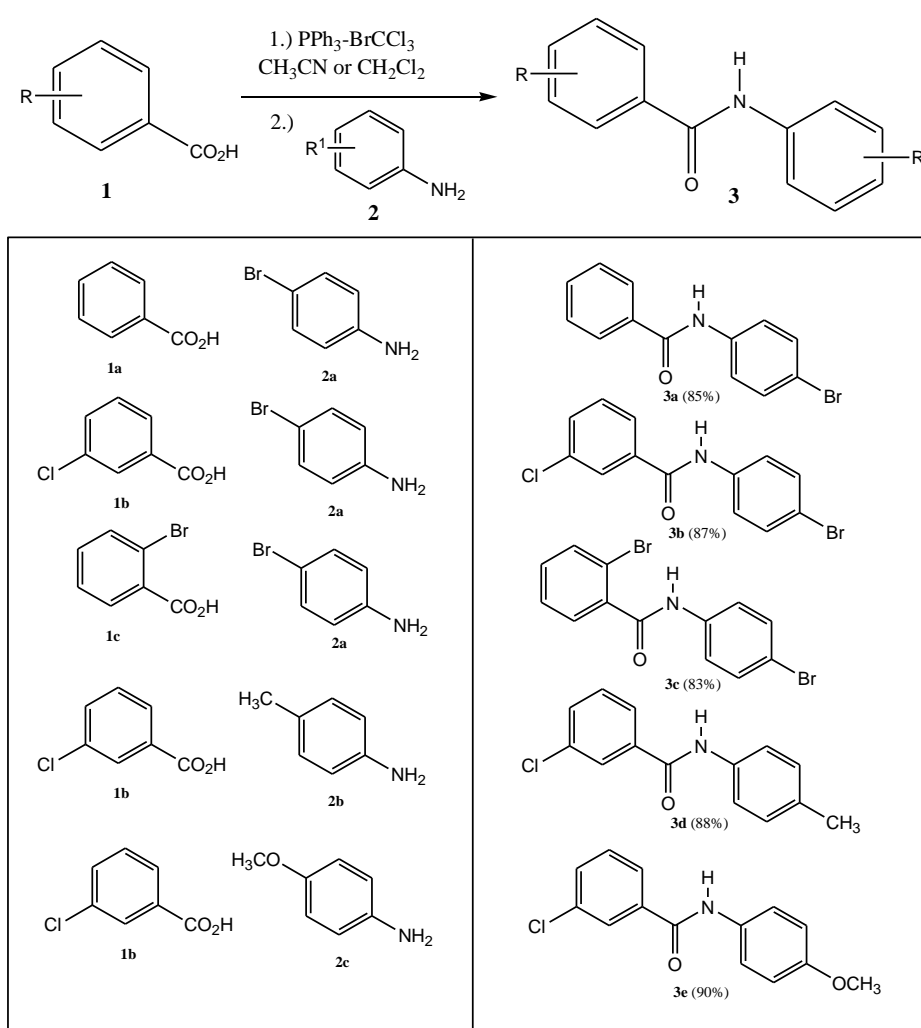


Table 1. Reaction of benzoic acids with anilines in the presence of $\text{PPh}_3\text{-BrCCl}_3$

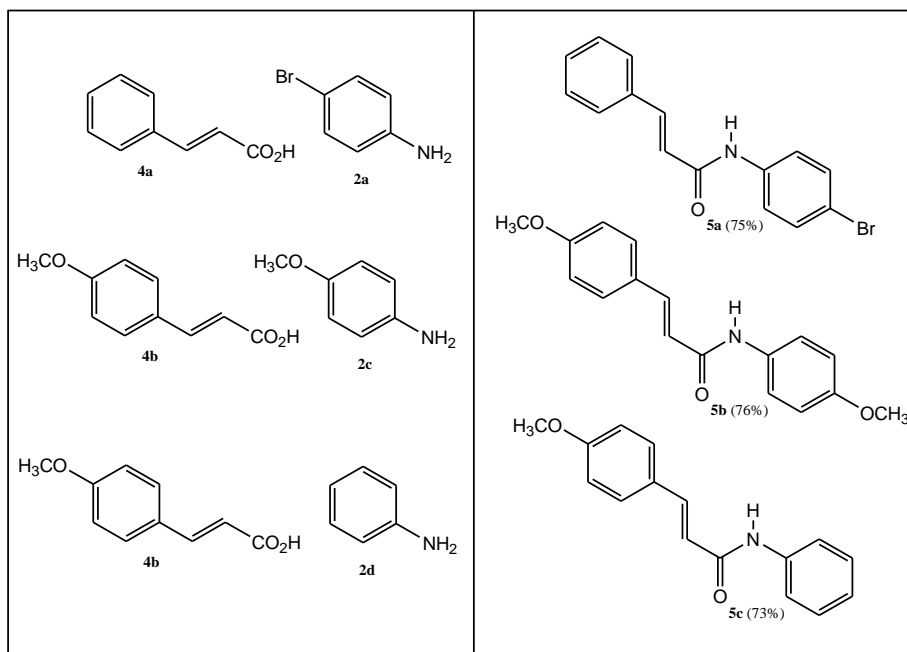
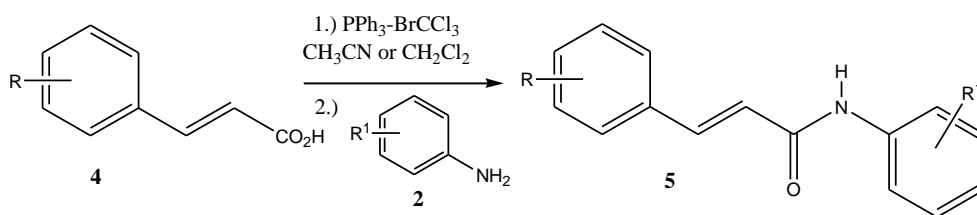


Table 2. Reaction of cinnamic acids with anilines in the presence of $\text{PPh}_3\text{-BrCCl}_3$

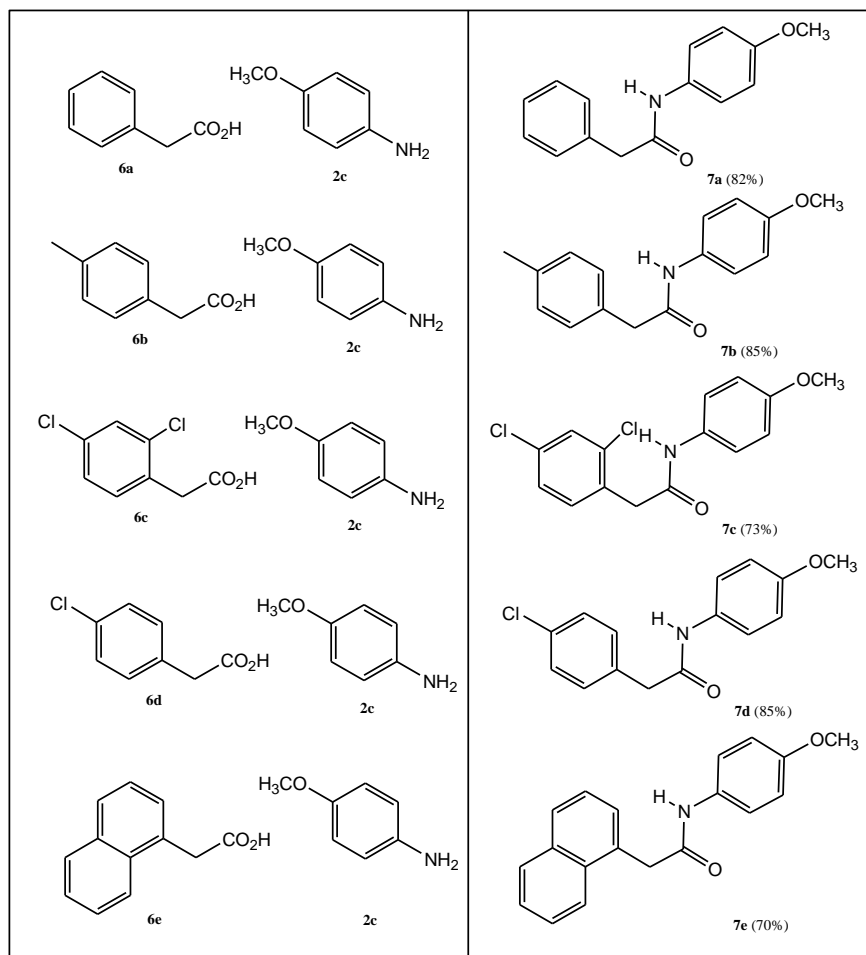
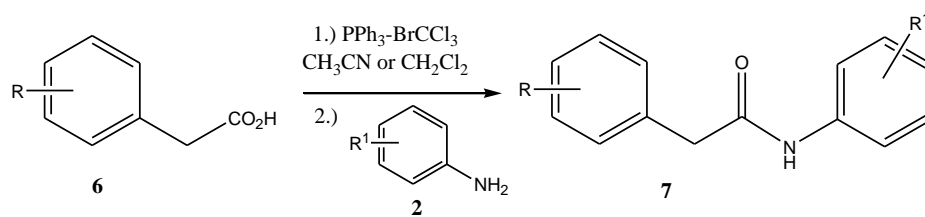
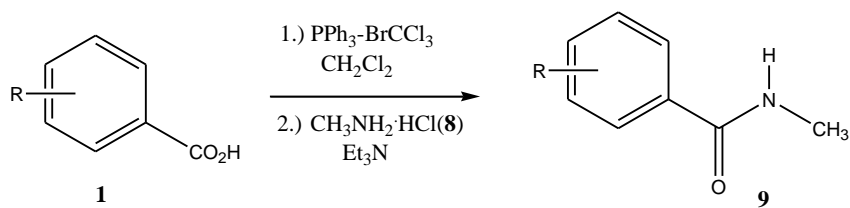


Table 3. Reaction of phenylacetic acids with anilines in the presence of $\text{PPh}_3\text{-BrCCl}_3$



<p>1b</p>	<p>CH₃NH₂·HCl 8</p>	<p>9a (83%)</p>
<p>1d</p>	<p>CH₃NH₂·HCl 8</p>	<p>9b (79%)</p>
<p>1e</p>	<p>CH₃NH₂·HCl 8</p>	<p>9c (70%)</p>
<p>1f</p>	<p>CH₃NH₂·HCl 8</p>	<p>9d (68%)</p>

Table 4. Reaction of substituted benzoic acids with methylammonium chloride in the presence of PPh₃-BrCCl₃

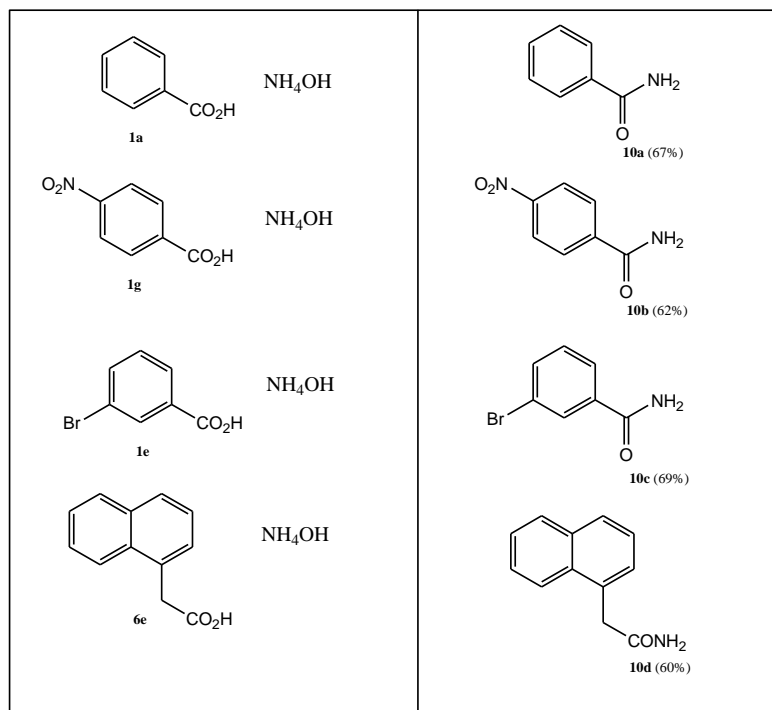
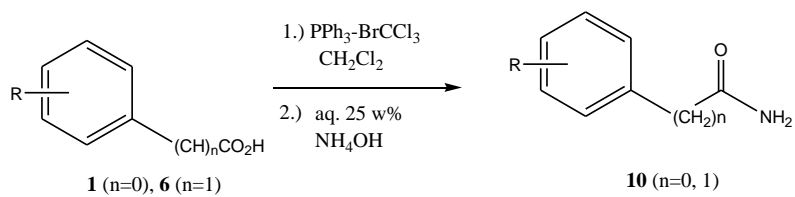


Table 5. Reaction of carboxylic acids with aq. ammonia in the presence of PPh₃-BrCCl₃

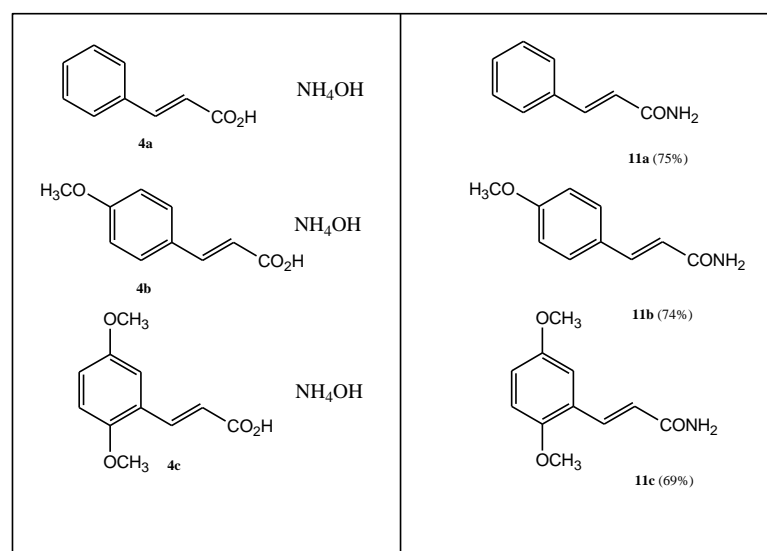
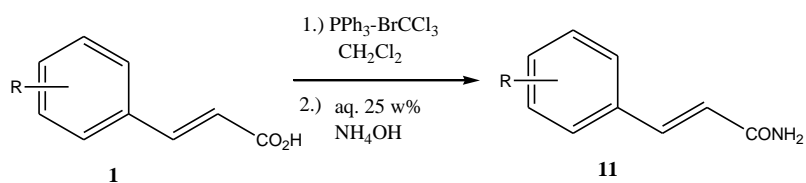


Table 6. Reaction of cinnamic acids with aq. ammonia in the presence of PPh₃-BrCCl₃

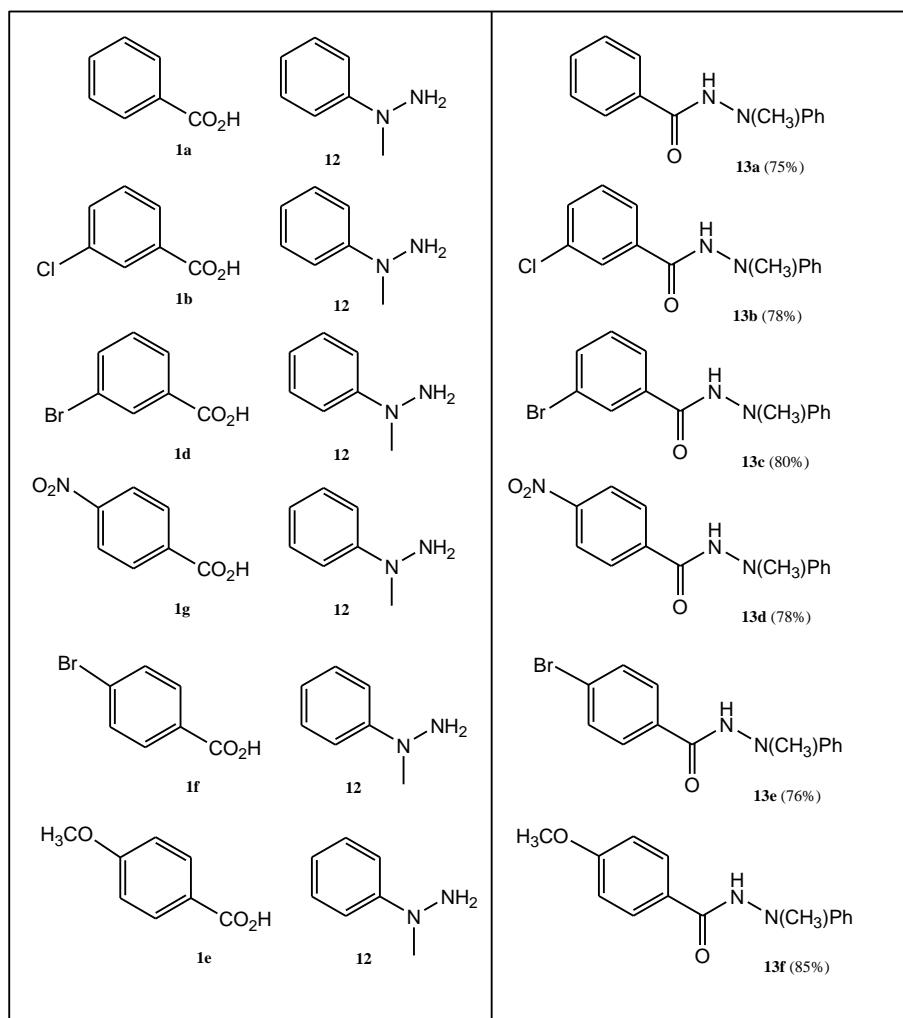
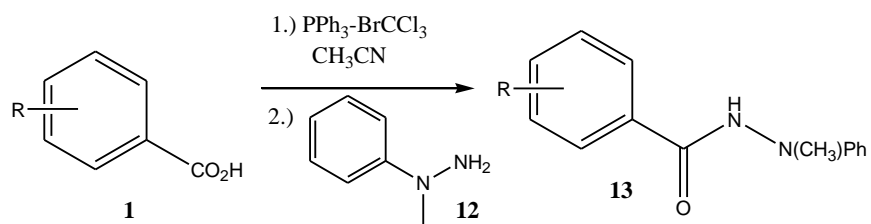


Table 7. Reaction of benzoic acids with 1-methyl-1-phenylhydrazine in the presence of PPh₃ – BrCCl₃.

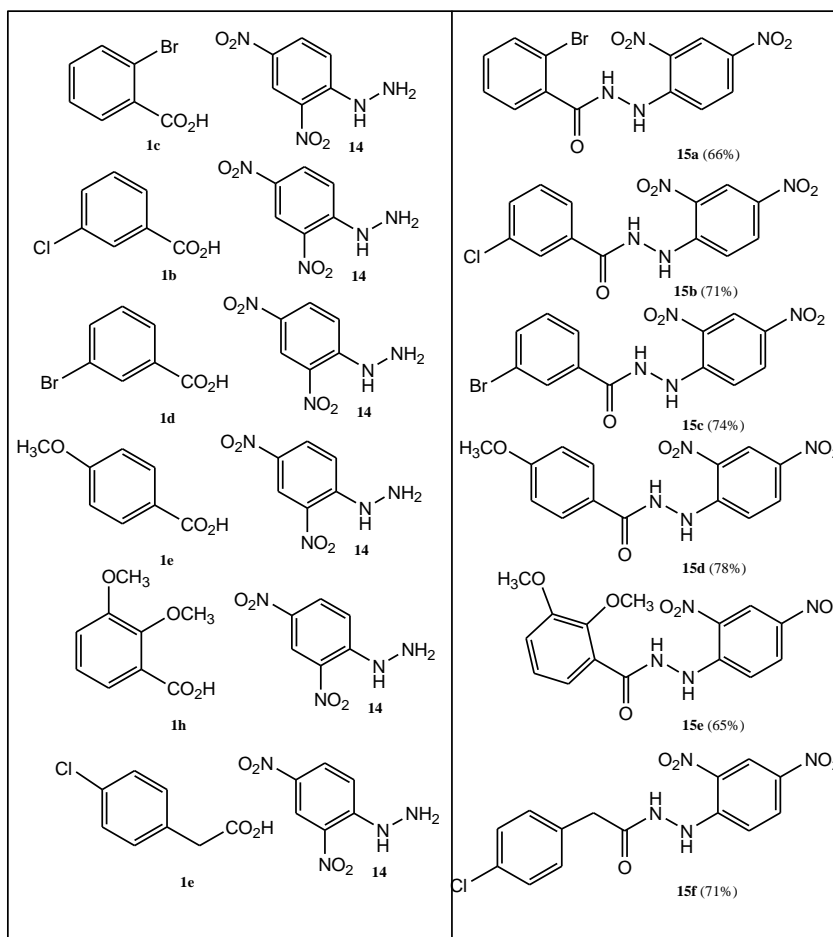
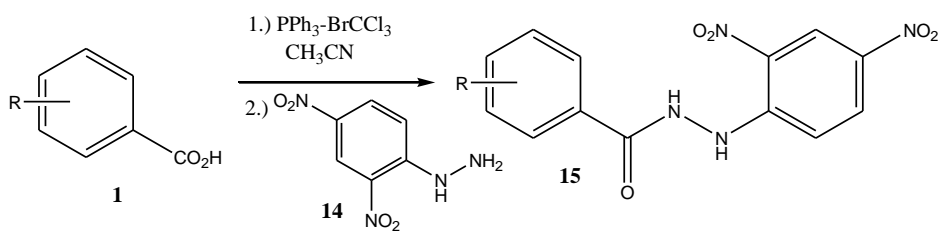


Table 8. Reaction of benzoic acids and 4-chlorophenylacetic acid with 2,4-dinitrophenylhydrazine in the presence of $\text{PPh}_3 - \text{BrCCl}_3$.

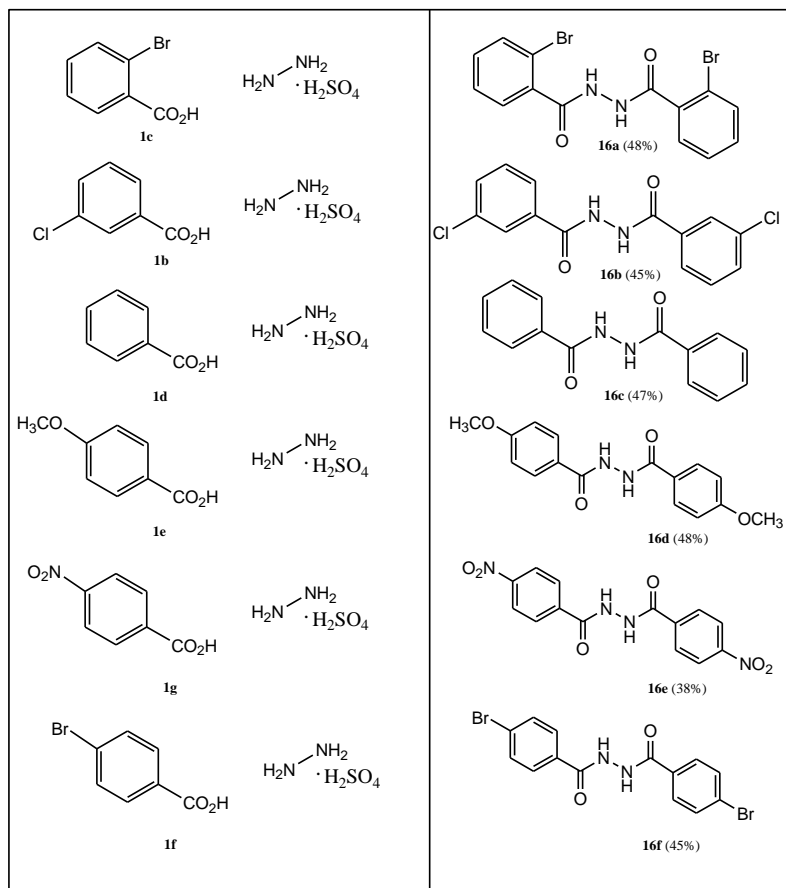
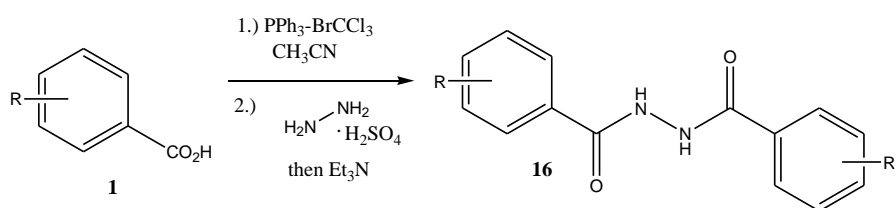


Table 9. Reaction of benzoic acids with *in situ* released hydrazine in the presence of $\text{PPh}_3 - \text{BrCCl}_3$ to yield 1,2-diacylhydrazines **16**.

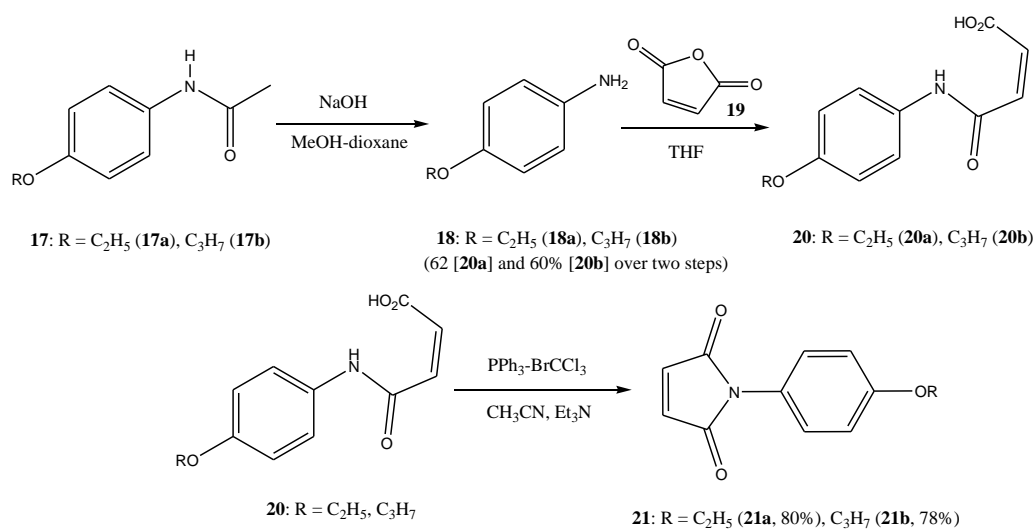


Table 10. Reaction of maleianilic acids **20** to *N*-arylmaleimides **21**.

5. Conclusion

In conclusion, it can be said that acyl halides, prepared *in situ* by the action of $\text{PPh}_3\text{-BrCCl}_3$ on carboxylic acids can be transformed further in one pot by the reaction with anilines and hydrazines to anilides and hydrazides, respectively. Also, ammonium and hydrazinium salts can be used when trimethylamine is added as base. Furthermore, the reaction of maleianilic acids with $\text{PPh}_3\text{-BrCCl}_3$ provides *N*-arylmaleimides.

Author Contributions: Conceptualization, supervision, investigation, writing—original draft preparation, T.T.; investigation, A.H.; investigation, A.H.; writing—review and partial supervision, M.B.

Conflicts of Interest: The authors declare no conflict of interest.

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