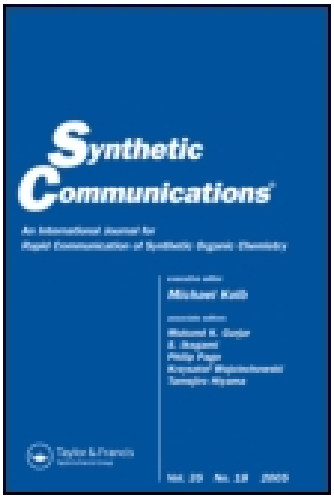

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Efficient One-Pot Friedel-Crafts Acylation of Benzene and its Derivatives with Unprotected Aminocarboxylic Acids in Polyphosphoric Acid

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Efficient One-Pot Friedel–Crafts Acylation of Benzene and its Derivatives with Unprotected Aminocarboxylic Acids in Polyphosphoric Acid

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Abstract: A number of aminobenzophenones have been synthesized by acylation of benzene and its derivatives with different 2-,3-,4-aminobenzoic and 4-aminophenylacetic acids in polyphosphoric acid via Friedel–Crafts reaction as compounds with expected antitumor activity.

Keywords: Aminobenzophenones, benzodiazepine intermediates, Friedel–Crafts acylation, nonlinear optic, polyphosphoric acid

INTRODUCTION

Nonlinear optical techniques are moving toward the goal of integrated, small-scale technology using high-intensity and broad spectrum band pass laser light. Organic molecules with an open electron shell and a conjugated donor-acceptor group often have large polarizabilities and hyperpolarizabilities. Such molecules exhibit nonlinear optical properties.[1] The most promising material of this type is 4-aminobenzophenone. These compounds had interesting photochromic properties at different conditions. The compounds change their color in a variety of solvents and pH values. Similar photoproperties have been reported for 4-methoxybenzophenone,[2]

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4-aminobenzophenone,[1] and ketoprofen[3] in a variety of solvents and pH values. For example, in air and under normal light conditions, 4-aminobenzophenone undergoes a color change from colorless to a deep pink color.[1] Benzophenone derivatives are also widely used in sunscreen lotions for ultraviolet A (UVA) protection.[4]

Besides, some benzophenones possess biological activity as sultam derivatives, for example, antitumor and anticonvulsive[5] activity against RNA virus hepatitis C.[6] They showed excellent cytotoxic activities against a panel of human cancer cell lines including multidrug-resistant cell lines.[7] 2-(4-Aminophenyl)-1-phenyl-ethanone also possess in vivo and in vitro activity as inhibitor of acyl-CoA–cholesterol acyltransferase (ACAT).[8] Besides benzophenones were intermediates in the synthesis of benzodiazepine derivatives[9] and were investigated in the research laboratories of Hoffman–La Roche.[10]

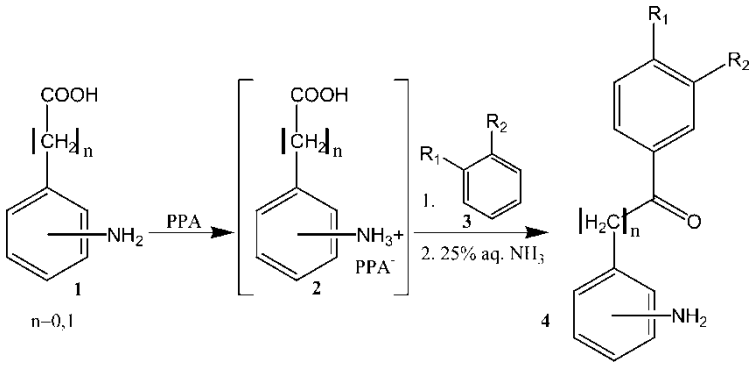
RESULTS AND DISCUSSION

In view of these observations, we had to synthesize different aminobenzophenones as compounds with interesting photochromic properties at different conditions and expected biological activity. Direct synthesis of aminobenzophenones by Friedel–Crafts acylation involves problems. Acylation of methoxybenzene with 4-nitrobenzoyl chloride followed by reduction of obtained 4-nitro-4-methoxybenzophenone gave 4-amino-4-methoxybenzophenone.[11] Some authors used a reaction of 4-substituted (chloro or nitro) anilines with benzoyl chlorides in the presence of zinc chloride under drastic conditions (heating at 200 to 230°C).[8]

The Friedel–Crafts acylation of activated benzene rings with various acylating agents such as benzamide, benzonitrile, ethyl benzoate, and benzoic acid in the presence of polyphosphoric acid (PPA) is the most used method for direct synthesis of aromatic ketones.[7,12] In a search of a new approach to isoquinolines we investigated the reaction of carboxylic acids, their esters, and anhydrides with 2-(3,4-dimethoxyphenyl)-ethylamine (homoveratrylamine) and its derivatives in PPA.[13] We found that this reaction afforded the corresponding 3,4-dihydroisoquinolines in good yields and purity.

In this article we applied this reaction to the synthesis of (4-aminophenyl)-(3,4-dimethoxyphenyl)-methanone (4-amino-3′,4′-dimethoxybenzophenone), known compound,[14] at first.

We found that when the dichloromethane solution of 4-aminobenzoic acid was carefully mixed in the presence of PPA, the ammonium salt **2** was obtained. Then adding of 1,2-dimethoxybenzene (veratrol) into the reaction mixture and heating at 80°C for 2 h led to the product with high yield (~79%) and purity (Scheme 1). These results prompted us to prepare differently substituted benzophenones (Table 1).

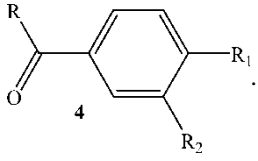


Scheme 1.

We found that benzophenones obtained from substituted benzenes with activated aromatic rings were prepared with higher yields than the same products prepared with unsubstituted benzene.

In conclusion we report for the first time application of carboxylic acids with unprotected amino groups in a Friedel–Crafts reaction with benzene and its derivatives. The synthesized compounds have potential biological activity. Some of them also possess interesting photochromic properties. This property

Table 1. Friedel–Crafts reaction of benzene and its derivatives with unprotected aminocarboxylic acids **4a–l**



Entry	R	R_1	R_2	Yield, %
4a	2-NH_2-C_6H_4	H	H	48
4b		MeO	H	75
4c		MeO	MeO	77
4d	3-NH_2-C_6H_4	H	H	49
4e		MeO	H	76
4f		MeO	MeO	78
4g	4-NH_2-C_6H_4	H	H	50
4h		MeO	H	75
4i		MeO	MeO	78
4g	4-NH_2-$C_6H_4CH_2$	H	H	52
4k		MeO	H	76
4l		MeO	MeO	78

of aminobenzophenones made them appropriate to use in nonlinear optics and in sunscreen lotions for UVA protection.

EXPERIMENTAL

Melting points were determined on a Boëtius hostage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were measured in Bruker-250 device by using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) were referenced to the chemical shifts of either TMS ($\delta = 0.00$ ppm) as an internal standard, and coupling constants are indicated in Hz. Mass spectra were recorded on a Jeol JMS-D300 spectrometer (70 eV). All new compounds had correct parent ion peaks by mass spectrometry. Polyphosphoric acid was obtained from 85% phosphoric acid and P_2O_5 (1:1 w/w).

General Procedure for the Preparation of Products 4a–l

Corresponding aminocarboxylic acid 3 mmol was dissolved in CH_2Cl_2 (3–5 mL) in an open flask, and polyphosphoric acid (10 g) was added. Then 3 mmol of benzene (or its substituted derivatives) was added. The mixture was stirred carefully at 80°C for 2 h and then poured on crushed ice. The solution was carefully alkalized with 25% ammonia and then extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and filtrated on a short column with basic Al_2O_3. The products, after evaporation of the solvent, were purified by recrystallization from MeOH.

Data

(2-Aminophenyl)-phenyl-methanone (4a): known compound, mp 103–107°C (lit.[15] mp 105–106°C).

(2-Aminophenyl)-(4-methoxyphenyl)-methanone (4b): known compound, mp 79–80°C (lit.[16] mp 78–80°C).

(2-Aminophenyl)-(3,4-dimethoxyphenyl)-methanone (4c): known compound, mp 74–76°C (lit.[17] mp 74–76°C).

(3-Aminophenyl)-phenyl-methanone (4d): mp 109–109.5°C; ^{1}H NMR ($CDCl_3$): 7.76–6.69 (m, 9H, Ar); 3.83 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): 194.7, 162.3; 151.4, 132.5, 131.9, 130.8, 129.6, 120.2, 113.6, 55.3. MS m/z: 197 (M^+); anal. calcd. for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.31; H, 5.73; N, 7.23.

(3-Aminophenyl)-(4-methoxyphenyl)-methanone (4e): mp 114–116°C; ^{1}H NMR ($CDCl_3$): 7.84–6.91 (m, 8H, Ar); 3.85 (s, 3H, OMe); 3.78 (br s,

2H, NH_2); ^{13}C NMR ($CDCl_3$): 195.7, 163.1, 146.9, 139.3, 132.4, 130.2, 128.9, 120.2, 119.6, 118.4, 115.6, 113.4, 111.4, 55.5. MS m/z: 227 (M^+); anal. calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.12; H, 5.92; N, 6.31.

(3-Aminophenyl)-(3,4-dimethoxyphenyl)-methanone (4f): mp 107–109°C; ^1H NMR ($CDCl_3$): 7.46–6.82 (m, 7H, Ar); 3.92 (s, 6H, 2 × OMe); 3.84 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): 195.7, 152.8, 148.8, 146.4, 139.2, 130.2, 128.8, 125.4, 120.6, 118.3, 115.6, 112.0, 109.6, 56.0. MS m/z: 257 (M^+); anal. calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.12; H, 6.03; N, 5.57.

(4-Aminophenyl)-phenyl-methanone (4g): known compound mp 107–110°C (lit.[18] mp 106–107°C).

(4-Aminophenyl)-(4-methoxyphenyl)-methanone (4h): known compound[11] mp 105–108°C.

(4-Aminophenyl)-(3,4-dimethoxyphenyl)-methanone (4i): known compound[14] mp 191–192°C; ^1H NMR ($CDCl_3$): 7.58–6.60 (m, 7H, Ar); 5.15 (br s, 2H, NH_2); 3.84 (s, 6H, 2 × OMe); ^{13}C NMR ($CDCl_3$): 193.4, 151.1, 132.1, 126.3, 123.7, 55.5, 39.6. MS m/z: 257 (M^+); anal. calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.15; H, 6.03; N, 5.58.

2-(4-Aminophenyl)-1-phenyl-ethanone (4g): mp 97–99°C; ^1H NMR ($CDCl_3$): 7.78–6.97 (m, 9H, Ar); 4.15 (br s, 2H, NH_2); 3.81 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$): 194.5, 162.3, 151.4, 131.5, 131.9, 130.8, 129.6, 120.2, 113.6, 55.3, 44.6. MS m/z: 211 (M^+); anal. calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.73; H, 6.35; N, 6.75.

2-(4-Aminophenyl)-1-(4-methoxyphenyl)-ethanone (4k): known compound[19] mp 89–90°C (lit. mp 89–92°C).

2-(4-Aminophenyl)-1-(3,4-dimethoxyphenyl)-ethanone (4l): mp 162–165°C; ^1H NMR ($CDCl_3$): 7.65–6.59 (m, 7H, Ar); 4.10 (s, 2H, CH_2); 3.91 (s, 6H, 2 × OMe); 3.60 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$): 194.7, 162.3, 156.7, 151.4, 132.5, 128.8, 127.7, 120.2, 113.6, 55.5. MS m/z: 271 (M^+); anal. calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.97; H, 6.44; N, 5.30.

REFERENCES

1. Pan, F.; Sherwood, J.; Simpson, G. Growth, perfection and properties of the organic nonlinear optical crystal, 4-aminobenzophenone (ABP). *J. Mater. Chem.* **1997**, *7*, 1383.
2. Bosca, F.; Cosa, G.; Miranda, M.; Scaiano, J. Inversion of 4-methoxybenzophenone triplet in aqueous solutions. *Photochem. Photobiol. Sci.* **2002**, *1*, 704.

3. Martinez, L. J.; Scaiano, J. C. Transient intermediates in the laser flash photolysis of ketoprofen in aqueous solutions: unusual photochemistry for the benzophenone chromophore. *J. Am. Chem. Soc.* **1997**, *119*, 11066.
4. Deleu, H.; Maes, A.; Roelandts, R. The relative importance of the components used for ultraviolet A protection in broad-spectrum sunscreens. *Photodermatol. Photoimmunol. Photomed.* **1992**, *9*, 29.
5. Doss, S.; Baghos, V.; Abdelhamid, A.; Halim, M. M. Synthesis of sultam derivatives with expected biological activity. *Molecules* **2000**, *5*, 816.
6. Wyss, D.; Arasappan, A.; Senior, M.; Wang, Y. S.; Beyer, B.; Njoroge, G.; McCoy, M. Non-peptidic small-molecule inhibitors of the single-chain hepatitis C virus NS3 protease/NS4A cofactor complex discovered by structure-based NMR screening. *J. Med. Chem.* **2004**, *47*, 2486.
7. Mahendra, M.; Doreswamy, B.; Sudha, B.; Khanum, S.; Shashikanth, S.; Sridhar, M.; Prasad, J. Synthesis and crystal structure of (3,4-dimethoxy phenyl)-(2-chlorophenyl)methanone. *Anal. Sci.* **2003**, *19*, 57.
8. Clader, J.; Berger, J.; Burrier, R.; Davis, H.; Domalski, M.; Dugar, S.; Kogan, T.; Salisbury, B.; Vaccaro, W. Substituted (1,2-diarylethyl)amide acyl-CoA:cholesterol acyltransferase inhibitors: Effect of polar group on in vitro and in vivo activity. *J. Med. Chem.* **1995**, *38*, 1600.
9. Sternbach, L. 1,4-Benzodiazepines: Chemistry and some aspects of the structure–activity relationship. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 34.
10. Sternbach, L.; Fryer, I.; Metlesics, W.; Sach, G.; Stempel, A. Quinazolines and 1,4-benzodiazepines, V: o-Aminobenzophenones. *J. Org. Chem.* **1962**, *27*, 3781.
11. (a) Shani, J.; Gazit, A.; Livshitz, T.; Biran, S. Synthesis and receptor-binding affinity of fluorotamoxifen, a possible estrogen-receptor imaging agent. *J. Med. Chem.* **1985**, *28*, 1504; (b) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. Aminohaloborane in organic synthesis,1: Specific ortho substitution reaction of anilines. *J. Am. Chem. Soc.* **1978**, *100*, 4842.
12. (a) Staskun, B. Nuclear acylation of arylamines. *J. Org. Chem.* **1964**, *29*, 2856; (b) Schellhammer, W. *Methoden der Organischen Chemie*; Müller, E., Ed.; Houben-Veyl: Thieme, Stuttgart, 1973; Vol. 7, p. 281.
13. Venkov, A.; Ivanov, I. Synthesis of isoquinolines from 2-phenylethylamines, amides, nitriles and carboxylic acids in polyphosphoric acid. *Tetrahedron* **1996**, *52*, 12299.
14. Model, E. Isoindolinone pigments made from tetraphenylketazine and their use. Patent DE 2903709, 1979; *Chem. Abstr.* **1979**, *91*, 212574.
15. (a) Ravi, S.; Saravanan, N.; Shanthi, A.; Dharmaraj, N.; Lakshmanan, A. Thermal Fries rearrangement of anilides. *Indian J. Chem. Sect. B* **1991**, *30*, 443; (b) Hu, W.; Guo, Z.; Chu, F.; Bai, A.; Yi, X.; Cheng, G.; Lib, J. Synthesis and biological evaluation of substituted 2-sulfonyl-phenyl-3-phenyl-indoles: A new series of selective COX-2 inhibitors. *Bioorg. Med. Chem.* **2003**, *11*, 1153.
16. (a) Olah, G. *Friedel–Crafts and Related Reactions*; Interscience: New York, London, Sydney, 1964; I–IV; (b) Simpson, J. C. E.; Atkinson, C. M.; Schofield, K.; Stephenson, O. *o*-Amino ketones of the acetophenone and benzophenone types. *J. Chem. Soc.* **1945**, 646.
17. Bowen, I. H.; Gupta, P.; Khan, M. S.; Lewis, J. R. Oxidative coupling, X: Cyclizations of 2-aminobenzophenones. *J. Chem. Soc.*, Perkin Trans. 1 **1972**, 2524.

18. Pratt, J. R.; Massey, W. D.; Pinkerton, F.; Thames, S. Organosilicon compounds, XX: Synthesis of aromatic diamines via trimethylsilyl-protecting aniline intermediates. *J. Org. Chem.* **1975**, *40*, 8.
19. Nave, P.; Trahanovsky, W. Oxidation of organic compounds with cerium(IV): Oxidative cleavage of 1,2-diarylethanols and 1-aryl-2,3-diphenylpropan-2-ols by cerium(IV) and chromic acid. *J. Am. Chem. Soc.* **1971**, *93*, 4536.