DIRECT SYNTHESIS OF SOME SUBSTITUTED 2- AND 4-AMINOBENZOPHENONES

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ABSTRACT
A number of 4-aminobenzophenones were obtained as compounds with expected properties in non-linear optical techniques. These compounds possessed interesting photochromic properties at different conditions (sun light irradiation, solvents etc.). They changed their color from colorless to deep-red in solutions. Also, these derivatives were needed as intermediates for the synthesis of benzodiazepine derivatives and as compounds with expected antitumor activity.

Keywords: non-linear optics, p-Aminobenzophenone, Synthesis, Benzodiazepine intermediates

INTRODUCTION
Non-linear optical techniques are developing towards 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 non-linear optical properties. For these materials non-linear efficiency varies with transparency since increasing the size of the conjugated electron system leads to a lowering of the energy of the excited state and increasing colouration. A survey of potential organic materials from this type using both theoretical and spectroscopic assessment has revealed the general suitability of 4-aminobenzene-carbonyl molecular types for this purpose [1].

The most promising material of this type is 4-aminobenzophenone. When irradiated by laser light, compounds based on this type of molecule show second harmonic generation, which has many technological applications in communications and optical data storage.

Besides, some benzophenones possess biological activity as sultam derivatives; e.g., antitumor, anticonvulsive [2] and activity against RNA virus hepatitis C [3].
Benzophenone derivatives are widely used in sunscreen lotions for Ultra Violet A (UVA) protection, also [4]. Benzophenone derivatives are useful for controlling phytopathogenic fungi and fungi diseases. For example (2,6-dichlorophenyl)-(2,5-dimethoxy-3-methylphenyl)-methanone; phenstatin, etc. have been found to be cytotoxic agents. They showed excellent cytotoxic activities against a panel of human cancer cell lines including multi-drug resistant cell lines [5].

RESULTS AND DISCUSSION

In view of these observations, we had to synthesize different aminobenzophenones as compounds with expected biological activity and properties in non-linear optics. Direct synthesis of these compounds by Friedel-Crafts acylation involves problems. Some authors have obtained derivatives indirect [6] applied Friedel-Crafts acylation of 4-nitrobenzoyl chloride with methoxybenzene. The reduction of obtained 4-nitro-4-methoxybenzophenone gave 4-amino-4-methoxybenzophenone. The Friedel-Crafts acylation of activated benzene rings in the presence of polyphosphoric acid (PPA) is the most possible method for direct synthesis of aromatic ketones [5,7]. In a search of a new approach for similar synthesis in our previous reports we investigated into the reaction of carboxylic acids with 2-(3,4-dimethoxyphenyl)-ethylamine (homoveratrylamine) and their derivatives in PPA for preparation of some isoquinoline derivatives [8]. We found that the reaction of equimolar amounts of homoveratrylamine with carboxylic acids in PPA for 2h at 80°C afforded very conveniently the corresponding 3,4-dihydroisoquinolines in very good yields and purity. The same reactions can also be carried out with esters and anhydrides of carboxylic acids. The successful application of this way to synthesis indicated to enlarge applications opportunities. In this paper we considered the possibility of acylation of benzene or some substituted benzenes 3 with 2- and 4-aminobenzoic acid 1 in the presence of PPA, which is a permanent interest in synthetic application of us. We applied this reaction for the synthesis of 4-amino-4-methoxybenzophenone at first. We assumed that when the dichloromethane solution of 4-aminobenzoic acid was carefully mixed in the presence of PPA at 80°C, the ammonium salt 2 was obtained. Then adding of methoxybenzene (anisol) into the reaction mixture and heating for 2h led to product in the reaction condition (Scheme 1) with high yield (75 %) and purity. These results prompted us to continue our research to prepare different benzophenones. By analogy we obtained benzophenones 4 of 2 or 4-aminobenzoic acid 1 and benzene derivatives 3. We found that benzophenones obtained from 2- or 4-aminobenzoic acid and substituted benzenes with activated aromatic rings were obtained with higher yields, than the same products prepared with unsubstituted benzene.
The products 4 change their color from colorless to deep-red in solutions. Similar photoproperties have been reported for 4-methoxybenzophenone [9], 4-aminobenzophenone [10], ketoprofen [11] in variety of solvents and pH values. For example in air and under normal light conditions, 4-aminobenzophenone undergoes color change from colorless to a deep-pink color [10]. Our pin-like crystals of benzophenones undergo the same color changes in solution (ethanol, CHCl₃ and CH₂Cl₂). We suppose that besides partial photolysis of the compound it undergoes a partial enolization. The coloration of benzophenones could be explained with an increasing the size of the conjugated π-electrons (in the enol form) leading to a lowering of the energy of the excited state, which additionally increases coloration of the compound.

In conclusion this property of benzophenones made them appropriate to use in non-linear optics and in sunscreen lotions for Ultra Violet A protection. Besides benzophenones were needed as intermediates for the synthesis of benzodiazepine derivatives and were investigated in research laboratories of Hoffman-La-Roche [12].

**EXPERIMENTAL**

Melting point was determined on a Boetius hostage apparatus and was uncorrected. Unless otherwise noted, NMR spectra were recorded on a Bruker 250 MHz devise by using CDCl₃ as solvent. Chemical shifts (δ, ppm) are downfield from TMS as an internal standard and coupling constants are in Hz. Polyphosphoric acid was obtained from 85% phosphoric acid and P₂O₅ (1:1 w/w).
Synthesis of substituted 2- and 4-aminobenzophenones; Typical procedure: 3 mmol 2-aminobenzoic (resp. 4-aminobenzoic) acid were dissolved in CH$_2$Cl$_2$ (3-5 ml) in an open flask and polyphosphoric acid (10 g) was added. Then 2 mmol of benzene (resp. substituted benzene) was added. The mixture was stirred carefully at 80 °C for 2h, then poured on crushed ice. The solution was carefully alkalized with ammonia, then extracted with CH$_2$Cl$_2$ (3x20 ml) and combines extracts were dried (Na$_2$SO$_4$) and filtrated on short column with basic Al$_2$O$_3$. The products, after evaporation of the solvent, were purified by recrystallization from MeOH.

Supporting Information Available: Chemical characterization data is available free of charge via the Department of Organic Chemistry.

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REFERENCES