SYNTHESIS AND FLUORESCENCE PROPERTIES OF 4-ACYL ISOCHROMAN-1,3-DIONES

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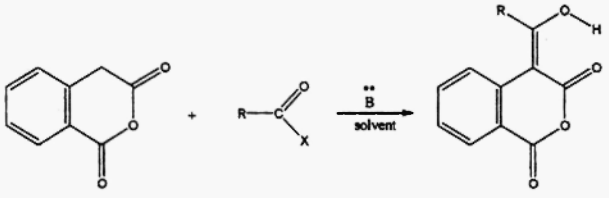
Abstract : 4-Acyl isochroman-1,3-diones are very difficult to obtain and they were not widely studied. We describe herein the best conditions of their preparation. The role of base, temperature and solvent are evidenced and described. Fluorescence properties of these compounds, not known up to now, are discussed. One of them displays dual fluorescence.

Key Words: Acylation; Homophtalic acid anhydride; HSAB-principle ; 4-Acyl isochroman-1,3-diones ; Fluorescence.

Introduction

4-Acyl isochroman-1, 3-diones are important heterocycles used as intermediates for the synthesis of 3-substituted isocoumarines (1)(2), isoquinolines (1)(3), isoquinolones, 2-carboxybenzyl alkyl ketones (4), etc. Recently, it was found that some natural derivatives of these compounds exhibited antimicrobial activities (5). They had been described since 1965 (6) but, only two methods were described by J. Schnekenburger (6) and by R. N. Usgaonkar et al.(1). Homophtalic anhydride (HPA) reacted with acid anhydrides or acid chlorides in presence of pyridine, yielding 4-acyl isochroman-1,3-diones (scheme 1).



Homophtalic anhydride 4-Acyl isochroman-1,3-dione

Scheme 1 : Formation of 4-Acyl isochroman-1,3-diones.

$X = OCOCH_3$, $R = CH_3$, $B = Py$;
$X = OCOC_6H_5$, $B = Py$, $R = C_6H_5$, solvent = chloroform ;
$X = Cl$, $R = C_6H_5$, $B = Py$, solvent = chloroform.

Before our works, the results for the synthesis of these compounds are poorly described in the literature, and the good yields obtained with acyl substituents (1), in comparison with the low yields (less than 20%) observed in the case of aroyl substituents (1)(6), could'nt be explain. Using the HSAB ("Hard and Soft Acid Base") principles requirement (7), we developed the reaction, selecting the best conditions to

obtain good yields with all type of substituents. As a part of our continuing investigations about the properties of these compounds, we report also herein the first study of their fluorescence spectra. It was found that the fluorescence properties of organic compounds, which display keto-enolic forms, can exhibit dual fluorescence (8) or reversible fluorescence (9) based on keto-enol tautomerism. Moreover, fluorescence properties of organic compounds can be used for investigation of molecular events in biological systems. Several applications such as artificial photosynthesis (10) molecular photovoltaic cells (11) and photo electronic devices (12) are emerging as an interesting field of research. Although a wide range of □-diketones and their keto-enol tautomerism have been studied extensively, little attention was paid to their fluorescence behaviour. In the following study, the R substituent effects on the fluorescence are examined.

Results And Discussion

1) Synthesis

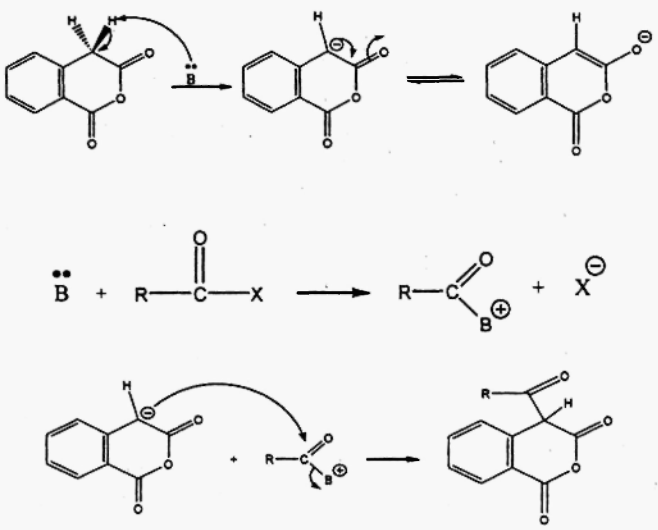
The mechanism of formation of 4-substituted isochroman-1,3-diones of which the structure is given above, is presumed to occur in four steps with the formation of acylating agent as reaction key (13) :

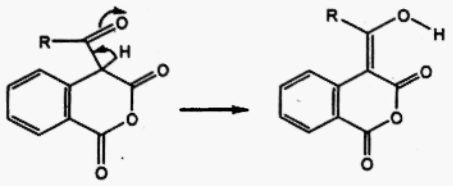
a - Formation of an anion from the homophtalic acid anhydride by an attack of the base on one of the protons of the active methylene group.

b - Formation of the acylating agent : one equivalent of base was used at the same time that the formation of the previous anion. Another equivalent is needed to form the acylating agent. So, at least, two equivalents of base are requiered.

c - Reaction of anion on the acylating agent :

d - Final prototropy giving 4-substituted isochroman-1,3-diones (scheme 2).





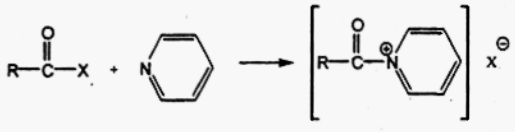
Scheme 2 : Mechanism of formation of 4-Acyl isochroman-1,3-diones.
B = Pyridine, N,N-dimethylaniline or Triethylamine; X = Cl or OCOR,
R = alkyl or aryl.

So, solvents (acetonitrile, diethyl ether, chloroform, dichloromethane, tetrahydrofuran), bases (pyridine, N,N-dimethylaniline and triethylamine), temperature (from -35°C to solvent reflux) and time of reaction have been modified with the aim to study their effects. Thus, the following results have been obtained.

- Compounds with R aliphatic (methyl and ethyl) are formed with more than 90% yield in diethyl ether with pyridine as base, at room temperature. They are colourless crystals.
- Compound with R = phenyl is formed as yellow crystal in diethyl ether with triethylamine (TEA) as base. It is necessary to reflux the mixture to obtain good yield.
- All other compounds with R aromatic are obtained as yellow or red crystals with TEA as base, at reflux of THF as solvent. Yields are quantitative.

We observed that when the acylating agent is an aliphatic compound, its formation takes place easily with pyridine at room temperature. Poor yield (<30%) is obtained by replacing pyridine by triethylamine. In the case of an aromatic compound, formation of acylating agent takes place with difficulty in the presence of pyridine or N,N-dimethylaniline but is easily obtained with triethylamine. It is necessary to work at the solvent reflux (scheme 3).

a)



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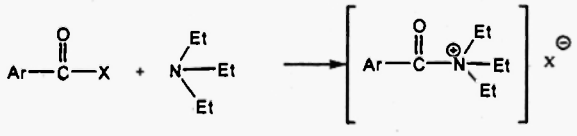
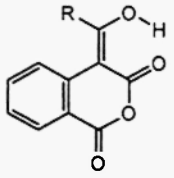


Scheme 3 :. a) X = OCOR or Cl ; b) OCOAr or Cl.

According to the HSAB theory (7), in acylation with aliphatic acyl groups, which are known to be soft acids, best results are obtained by using soft bases like pyridine (14). To obtain good acylation with hard acids, like aroyl groups, it is necessary to use hard bases like triethylamine (TEA). It was found that triethylamine is hard base while pyridine and N,N-dimethylaniline are soft bases (14). So, the nature of the base

must be suitable to the nature of acylating agent. The best solvents are ethers: diethyl ether or tetrahydrofuran (THF). In the case of an aromatic acylating reagent, it is also necessary to raise the temperature at solvent reflux.

Only three compounds R = CH_3, C_6H_5 (6) and C_3H_7 (1)(3) were described before our investigations. We prepared more than ten compounds and we studied their structures (15)(16)(17). Their physical and spectroscopic data (IR, ^1H, ^{13}C and ^{17}O NMR,) were consistent with the reported ones (17). The mass spectra of these compounds showed the good molecular peak for each of them, M-18 peak for 1 and 2 (R = aliphatic) and M-17 peak for the others (R = aryl), respectively for the lost of H_2O and the lost of the radical OH (18). For study their fluorescence properties, we selected the following compounds:



1 : R – CH_3; 2 : R = C_2H_5; 3 : R – C_6H_5;
4 : R = $pCH_3OC_6H_4$; 5 : R = $pNO_2C_6H_4$; 6 : R = pFC_6H_4;
7 : R = $pClC_6H_4$; 8 : R = $ptBuC_6H_4$; 9 : R = $p(CH_3)_2NC_6H_4$; 10 : R = $pCNC_6H_4$.

2) Fluorescence properties

The fluorescence spectra were recorded in DMSO solutions. Results are given in fig.1.

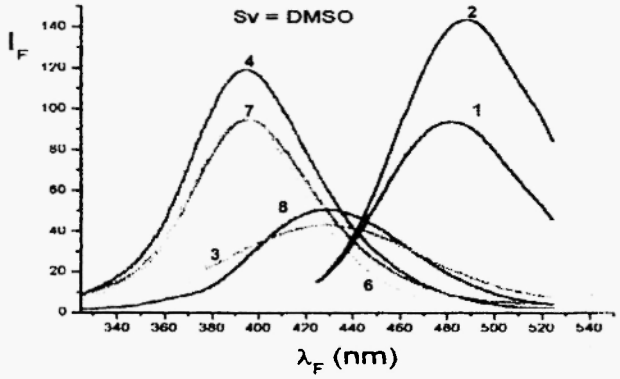


Fig.1
Fluorescence spectra of isochroman-1,3-diones in DMSO
1: R = CH_3 ; 2 : R = C_2H_5 ; 3 : R = C_6H_5 ; 4 : R = $pCH_3OC_6H_4$;
6 : R = pFC_6H_4 ; 7 : R = $pClC_6H_4$; 8 : R = $ptBuC_6H_4$.

All the compounds studied exhibit fluorescence, except compounds 5 and 10, respectively when R = p-nitrophenyl and R = p-cyanophenyl. This is due to the high

withdrawing effect of nitro and cyano groups. In the other cases, fluorescence is obtained and the below behaviours have been observed:

When R is an aromatic moiety, the wavelength of the fluorescence (λ_F) of isochroman-1,3-diones is shorter than 450 nm. (380 nm $\leq \lambda_F \leq$ 450 nm).

- When R is an aliphatic moiety, a bathochromic effect is obtained. The wavelength of fluorescence (λ_F) is longer than 450 nm (450 nm$< \lambda_F \leq$ 490 nm). In this case, the intensity of the fluorescence of 2 is higher than that of 1.
- In the case of an aromatic moiety, para substitution, exercises a noticeable influence over the fluorescence intensity.

* So, for a para hydrogen, the fluorescence wavelength is longer (λ_F = 423 nm) than for the other groups. The shortest wavelength is obtained for a para methoxy group, (λ_F = 406 nm).
* The intensity of the fluorescence increases with the donating character of para substituent. So, it is high in the cases of $pCH_3OC_6H_4$ or $p(CH_3)_2NC_6H_4$ groups and weak in the case of $ptBuC_6H_4$ or phenyl substituents. No fluorescence is obtained in the cases of 5 and 10 and no reversible fluorescence is observed for any compound.
* An original behaviour has been obtained in the case of the compound 9, R = $p(CH_3)_2NC_6H_4$ (Fig. 2). Its fluorescence spectrum displays a dual band. The two bands of fluorescence are largely separated. The first one is observed at 420 nm and the second one at 520 nm. This later band is more intense than the first one.

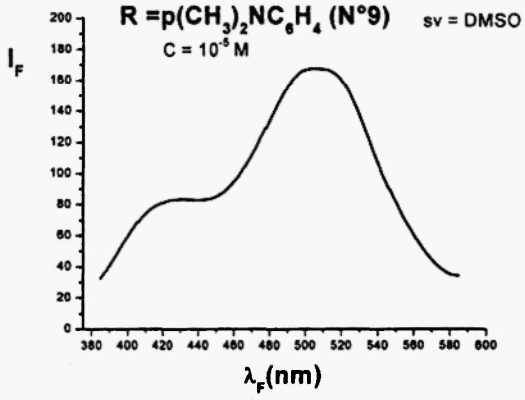


Fig. 2: Fluorescence spectrum of 9

* So, the titled isochromandiones with the substituants R = para dialkyaminophenyl moiety, should be a new class of dyes displaying dual fluorescence. It had been indicated that this probe was especially of interest in cellular and tissular studies where the local concentrations of dyes cannot be controlled (11). This fluorescence behaviour of organic compounds was explained by the possibility of an Excited State Intra-molecular Proton Transfer (ESIPT) reaction (19)(20)(21).

Conclusion

For the synthesis of 4-Acyl isochroman-1,3-diones by acylation of homophtalic acid anhydride (HPA) with aliphatic acid derivatives, it is necessary to use soft bases like pyridine in diethyl ether. If aroylation is needed, triethylamine (TEA) is recommended as base and THF as solvent. In this case, it is necessary to raise the reaction temperature to solvent reflux. It has been observed that ethers (diethyl ether

or tetrahydrofuran) give the best yields. These results are found to be suitable with HSAB theory. All the compounds are fluorescent except the compounds with p-nitrophenyl and p-cyanophenyl as substituents R. Bathochromic effect is obtained when the aromatic substituent (Ar) is replaced by an aliphatic one (R). The fluorescence intensity is also influenced by the electronic properties of the substituents. When substituents present a great withdrawing character, compounds are not fluorescent. In the case of donating substituents, the fluorescence intensity is correlated to the donating character of the substituents. This behaviour is observed in both cases, when R is aliphatic and when R is aromatic. Moreover, the compound with R = p-$(CH_3)_2NC_6H_4$ displays a dual fluorescence.

Experimental

Synthesis

Preparation of 4-Acyl isochroman-1,3-diones 1 and 2.

In a 500 ml flask fitted with water condenser, are introduced 300 ml of dried diethyl ether, 0.125 mole of aliphatic acid anhydride (or aliphatic acid chloride) and 4 ml of dried pyridine. Stirring the mixture, 0.12 mole of homophtalic anhydride is added by small portions of 0.03 mole, during 30 min. After this addition, the mixture is stirred at room temperature during 3 hours. The precipitate is filtered, washed with petroleum ether to remove the pyridine and is recrystallized in a mixture of chloroform and pentane. Yields are quantitative.

1: R = CH_3: 98%. (IR, KBr): 1740cm^{-1}; ^1H (NMR 60Mhz, $CDCl_3$): □ = 8.2 (□, 1H); □ = 7.1-7.8 (m, 3H); □ = 6.8 (m, 1H); □ = 2.7 (s, 3H).

2: R = C_2H_5: 93%. (IR, KBr): 1730cm^{-1}; ^1H (NMR, 60MHz, $CDCl_3$): □ = 8.2 (d, 1H); □ = 7.3-7.8 (m, 3H); □ = 6.9 (m, 1H); □ = 2.9 (q, 2H); □ = 1.6 (t, 3H).

Preparation of 4-Benzoyl isochroman-1,3-dione (R = C_6H_5) 3.

In a 250 ml flask fitted with water condenser, are introduced 100 ml of dried diethyl ether, 0.05 mole of benzoic acid anhydride (or benzoic acid chloride) and 25 ml of dried triethylamine. The mixture is stirred and 0.05 mole of homophtalic anhydride is added by small portions. The mixture is kept under agitation at room temperature during 1.5 hour and refluxed for 1.5 hour. The mixture is poured in a 1000 ml separatory funnel containing 300 ml of chloroform, washed with diluted hydrochloric acid solution until pH = 2 and with water to neutrality. Organic layer is dried over $MgSO_4$ and the solvent removed. The crude product is recrystallized in a mixture of dichloromethane and hexane. Yield is quantitative.

3: R = C_6H_5: 95%. (IR, KBr) 1760cm^{-1}; ^1H (NMR, 60MHz, $CDCl_3$): □ = 8.2 (m, 2H); □ = 7.2-7.7 (m, 7H); □ = 6.8 (m, 1H);

Preparation of other 4-Aroyl isochroman-1,3-diones (R = pXC_6H_4) 4, 5, 6, 7, 8, 9, 10.

To a solution of 4.10^{-2} mole of parasubstituted benzoyl chloride (or its anhydride) in 150 ml of dried THF, is added 0.12 mole of TEA and 4.10^{-2} mole of HPA by small portions during 30 min. The mixture is then refluxed for 2 or 3 hours and poured in 300 ml of chloroform. The solution is treated with dilute hydrochloric acid until the pH become acid (2 or 3). The organic layer is extracted, washed with water, dried over $MgSO_4$ and the solvent removed. The crude product is recrystallized in dichloromethane-pentane or chloroform-pentane. Good yields are obtained.

4: R = p$CH_3OC_6H_4$: 85%. (IR, KBr) 1762cm^{-1} ; ^1H (NMR, 60MHz, $CDCl_3$): □ = 8.0

(m, 2H); □= 6.9-7.5 (m, 6H); □ = 6.8 (m, 1H); □ = 3.3 (s, 3H).
5: R = $pNO_2C_6H_4$: 93%. (IR KBr) 1762cm^{-1}; ^1H (NMR, 60MHz, $CDCl_3$): □ = 8.2-8.3 (m, 2H); □ = 7.5-8.2 (m, 6H); □ = 6.9 (m, 1H).
6: R = pFC_6H_4: 85%. (IR, KBr) 1766cm^{-1}; H (NMR, 60MHz, $CDCl_3$:□ = 8.1 (m, 1H); □ = 7.2- 7.7 (m, 7H); □ = 6.8 (m, 1H).
7: R = $pClC_6H_4$: 90%. (IR, KBr) 1761cm^{-1}; ^1H (NMR, 60MHz, $CDCl_3$): □ = 8 (m, 2H); □ = 7.3-7.5 (m, 6H); □ = 6.8 (m, 1H).
8: R = $ptBuC_6H_4$: 60%. (IR, KBr) 1766cm^{-1}; ^1H (NMR, 60MHz, $CDCl_3$):□ = 8 (m, 2H); □ = 7.2- 7.5 (m, 6H); □ = 6.9 (m, 1H); □ = 1.3 (s, 9H).
9: R = p $(CH_3)_2NC_6H_4$: 70%. (IR, KBr) 1725 cm^{-1}; ^1H (NMR), 60 MHz, $CDCl_3$) :□ = 8,1 (m, 2H); □ = 6,9-7,8, (m, 6H); □ = 6,7 (m, 1H); □ = 2,6 (s, 6H).
10: R = $pCNC_6H_4$: 82% (IR, KBr) 1765cm^{-1}; 2233 cm^{-1} ; (^1H NMR, DMSO) :□ = 8.2 (m 2H); □ = 7.3-7.8 (m 6H); □ = 6.9 (m, 1H).

Fluorescence

All the fluorescence spectra have been recorded at room temperature with 10^{-4} mole/l solution (unless the case of 9) in analytical-grade DMSO, on a Kontron SFM-25 Spectrofluorometer.

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