Reactions of Fulgides: Regioselectivety in the Ring Opening Reactions of Unsymmetrical Bis-substituted dimethylene-succinic Anhydrides with Nucleophiles

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Summary:Nucleophiles were added regioselectivety on the carbonyl group in conjugation with the diphenyl methylene group of fulgide **1**, however in the heterocyclic fulgides such as **9a** and **10a** the addition takes place on the carbonyl group not in conjugation with the heterocycle ring. The addition of dicyanomethyl anion to heterocyclic fulgides resulted in novel photochromic derivatives **12a** and **12b** having an absorption maxima for the coloured forms above 620 nm.

Introduction

Since the discovery of fulgides or bis-substituted methylene succinic anhydrides at the beginnig of this century by Stobbe [1], many new fulgides were synthesised [2]. Fulgides **1** upon irradiation with ultraviolet light undergoes a conrotatory ring closure to the more coloured forms **2**. The latter can be reverts back to the original fulgide **1** when exposed to white light [3].

Although fulgides have been developed and investigated as functional elements in opto-optical switches [4-6], however reports on reactions of fulgides with nucleophiles are rear.

As part of our long standing interest in the synthesis and developments of novel fulgides and their derivatives as photochromic compounds to be used in the field of data storage and some other areas, the present paper describe the addition of different neucleophiles to unsymmetrical fulgides to establish which carbonyl group is more susceptible to neucleophilic addition.

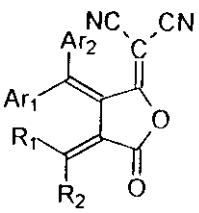
Results and Discussion

Two factos electronic vs steric control are needed to be considered in determination of the site of preferentially attack on one of the two carbonyls of the unsymmetrical fulgides.

In electronic control, theoretically attack was most likely on the carbonyl which more electron-deficient. This would depend on respective a,b-unsaturated carbonyl system. The greater the

electron-withdrawing ability of the group, the more likely nucleophilic attack occur at this carbonyl [7-8]. In the steric control, the approach had been shown for unsymmetrical anhydrides to occur via the "Burgi-Dunitz" angle (formula 6) [9-11].

Recently [12], it has been shown that the dicyanomethyl anion (generated *in situ*) attacks exclusively the diarylmethylene (alkylidene) succinic anhydrides at the carbonyl group in conjugation with the diarylmethylene group to give after cyclization compounds represented by the formula 7 as proved by x-ray crystal structure



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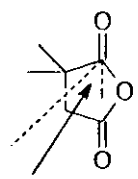
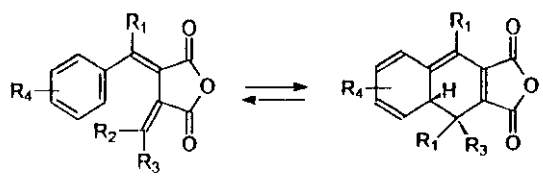


Burgi-Duntiz angle 6

Molecular modeling of fulgide **3** has shown that, the diphenylmethylene group lies out of the plane of the anhydride ring due to molecular over-crowing. Hence it is less able to donate electrons,

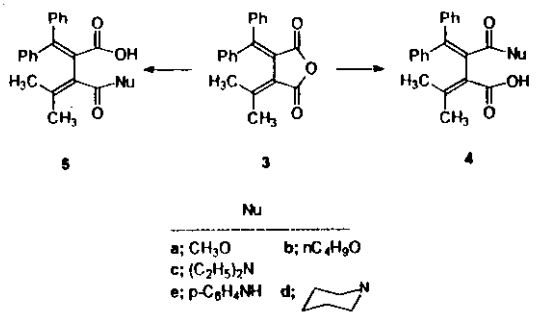


1 2

Scheme 1

unlike the carbonyl adjacent to the isopropylidene group. Attack is favored at this electron-deficient carbonyl. To get further insight on the regioselectivety of the ring opening reaction of fulgides, we reacted fulgide **3** with different nucleophiles namely sodium methoxide, *n*-butyl alcohol, pipyridene, diethylamine and *p*-toluidine (Scheme-2).

Compound **4a** was obtained upon treatment of fulgide **3** with sodium methoxide in methanol. The structure of compound **4a** was confirmed by comparing its spectral data with authentic sample obtained



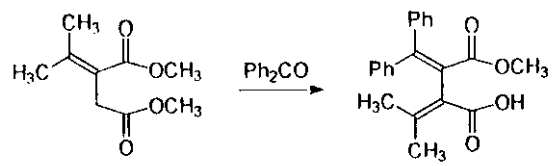
5 3 4

Nu

a; CH_3O b; nC_4H_9O
c; $(C_2H_5)_2N$
e; p-C_6H_4NH d;

Scheme 2

by the well-established Stobbe condensation product obtained from dimethyl isopropylidenesuccinate **8** and benzophenone (Scheme-3) [13]. On the other hand compound **4b** was prepared from fulgide **3** and *n*-butyl alcohol in the presence of small amount of hydrochloric acid. The mass spectrum of compound **4b** showed the base peak m/z 378 correspond to the molecular ion and an intense peak at m/z 304 which correspond to fulgide **3**.



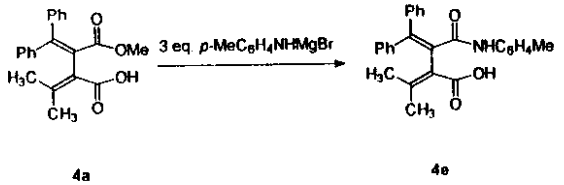
8 4a

Scheme 3

In addition compounds **4c-e** were prepared by stirring an equimolar quantity of fulgide **3** and the corresponding amine in THF at room temperature.

The structure of the succinamic acid **4e** was confirmed by comparing its spectral data with authentic sample obtained via different reaction pathway (Scheme 4) [14]. In the nmr spectra it is worthnoticing that, the isopropylidene methyl signals are apart 1.0 ppm in fulgide **3**, where in the open forms of the prepared half-esters **4a-b**, the separation between the two methyl isgnals is decrease to 0.3 ppm. On the other had in the succinamic acid **4c-d**, the two methyl signals of the isopropylidene group exhibited almost no separation (Table-1).

In the compound series **4a-e**, the electronif factor was dominated and the attack always took



4a 4e

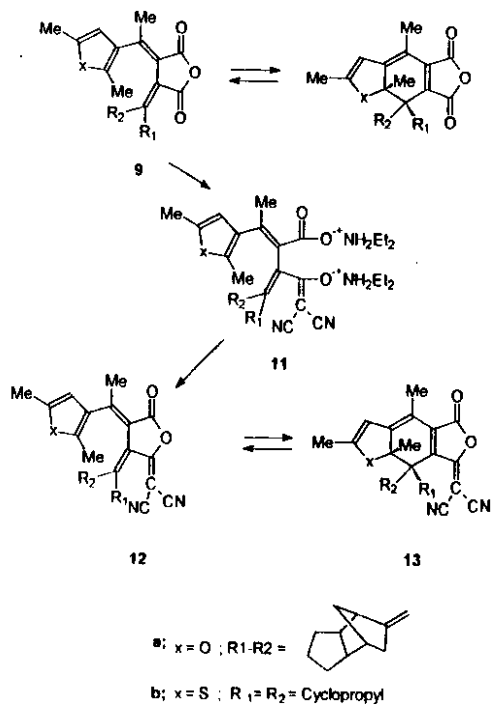
Scheme 4

Table-1: ^{1}H-NMR Spectral data of fulgide **3** and compounds **4a-e**

Comp. No.	CH_3 trans to C=O	CH_3 cis to C=O	Aromatic signals	Others
3	1.28	2.20	7.1-7.0	
4a	1.75	2.05	7.0-7.70	3.49 (3H, s, MeO)
4b	1.74	2.04	7.10-7.30	0.8 (3H,t), 1.08 (2H,m), 1.28 (2H,m), 3.9 (2H,t)
4c	1.90	1.96	7.06-7.36	1.18-1.55(6H,m),3.28-3.66(4H,m)
4d	1.88	1.92	7.06-7.33	0.66(3H,m), 1.0(3H,t), 2.91, 3.18, 3.5 (2H,m)
4e	1.88	2.01	7.0-7.40	2.27 (3H, s, *p*-Meph)

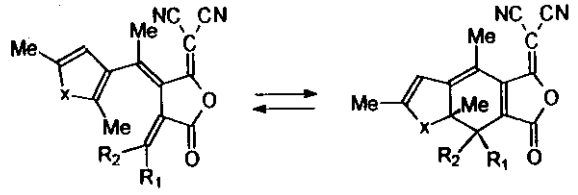
place on the carbonyl group conjugated to the dipehnylmethylene group. It was of interest to get deep understanding of the two factors governing the ring opening of unsymmetrical fulgides, so extend the work to include heterocyclic fulgides instead of the diphenylmethylene. For this two fulgides **9a** and **10a** containing furyl and thienyl groups respectively was selected.

It has been reported that the heterocyclic ring of hterocyclic fulgides lies co-planer with the anhydride ring, so that the electronic density could be migrated from the heterocyclic ring to the carbonyl in conjugation with it. Compared to the inductive effect of the other group i.e. the tricyclic moiety in **9a** and the dicyclopropylmethylene in **9b**. To examine this principle, the dicyanomethylene derivative **12a** and **12b** were synthesized according to a procedure described by Moor and Kim [15] for the synthesis of 3-dicyanomethylene phthalide by base-catalyzed condensation of phthalic anhydride with malononitrile. So equimolar quantity of gulgide **9a** and **9b** and malononitrile in the presence of two molar equivalent of diethyl amine as base were stirred to give the disalts **11a** and **11b** respectively. The latters were on cyclization using acetyl chloride afforded the novel series of photochromic derivatives of fulgides 12a and **12b** respctively. In fulgides **9a** and **9b** the nucleophilic attack is believed to occur on the carbonyl group not on conjugation with heterocyclic rings. This suggestion was farified from the fact that, the colour of cyclized forms of the novel derivatives **12a** and **12b** i.e. **13a** and **13b** respectively is blue compared to the red colour of the cyclized forms of their counter parts fulgides **9a** and **9b** i.e. **10a** and **10b** (Scheme-5).This deepening in the colour is due to the presence of the dicyanomethylene moiety in conugation with the rest of the chromophor. On the other hand, the other possibility of the nucleophilic attack which would ocurred on the carbonyl group in conjugation with the heterocyclic ring (i.e. the formation of derivative **14**) is ruled out because the colour of the cyclized form **15** (Scheme-6) is expected to be red since it contains the same chromophore as that of compound **10**. Table-2 summarizes the electronic spectral data of flugies **9a, 9b, 12a, 12b** and their cyclized forms **10a, 10b, 13a** and **13b**. The large bathochromic shift of the coloured forms of derivative **12a** and **12b** is attributed to the excellent electron withdrawing ability of the dicyanomethylene moiety.



Scheme 5

Electronic factor predominant the nucleophilic attack in the case of fulgides **3,9a** and **9b**. As final example the nucleophilic addition of dicyanomethyl anion to the monosubstituted succinic



14 15

Scheme 6

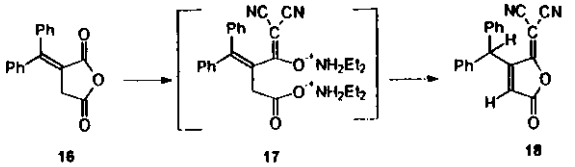
Table-2: UV-Visible spectral data of compounds **9a-b, 10a-b,12a-b and 13a-b**

Comp. No.	λ_{max} uncoloured form	Comp. No.	λ_{max} coloured form	λ
9a	346	**10a**	513	
9b	351	**10b**	542	
12a	385	**13a**	630	117
12b	390	**13b**	631	89

$\lambda = \lambda_{max}$ **(13a-b)** - λ_{max} **(10a-b)**

anhydride **16** was investigated to establish whether steric or electronic factors will favor the nucleophilic attack.

The nucleophilic attack by the dicyano-methylene is believed to take place on the carbonyl group in conjugation with the diphenylmethylene group. This was based on the electronic effects brought about by the two phenyl groups. Moreover, the product obtained was not ehe expected **17** but the 1,3 hydrogen shift adduct **18** as established from the ^{1}H-NMR spectra which showed two singlets at 5.35 and 4.15 ppm (Scheme-7). The two singlets are attributed to the methyl and the oliefinic protons respectively. Second evidence for the formation of the intermediate **17** is the red colouration of the solution developed when acetyl chloride was added. Similar colouration was observed when the colourless crystals of compounds having the general formula 7 were dissolved in organic solvents such as dichloro-methane or acetone the solutions are red. This phenomenon is due to the crystal backing as described by the author based on x-ray data of analogous compounds [12]. In the crystal state the two phenyl groups are folded and the one cis to the dicyanomethylene group lies on top of the cyano group close to it. Where as in solutions the two phenyl groups are twisted resulted in colouration.



16 17 18

Scheme 7

In conclusion the electronic factor is predominant in the ring opening reactions of unsymmetrical fulgides with nucleophiles.

Experimental

Melting points were recorded on a Thomas-Hoover capillary melting apparatus without correction. IR spectra were taken as KBr disk on a Nicolet Magna 520 FTIR spectrometer, ^{1}H-NMR were recorded in $CDCl_3$ on a Bruker DPX 400 spectrometer using TMS as internal standard. Mass spectra were obtained on a Varian MAT CH5 Spectrometer using EI technique. UV-visible spectra were recorded on a Shimadzu 260 spectrometer for solutions ($1x10^{-4}$M).

Diphenylmethylene(isopropylidene)succinic anhydride **3**.

This fulgide was available sample prepared by the author in previous work [13].

(5,6-Trimethylene-2-norbornylidene)-(E)-a-(2,5-dimethyl-3-furyl)ethylidenesuccinic anhydride **9a**

This fulgide was prepared in 25% overall yield by two successive Stobbe condensation of dimethyl succinate and 5,6-trimethylen-2-norbornanone and then 3-acetyl-2,5-dimethylfuran respectively using the modified procedure previously described by the author [14] yellow crystals, mp 150-152°C (from ethanol); (Found: C, 74.82; H, 6.52. $C_{22}H_{24}O_4$ requires C, 75.01; H, 6.81%); ^{1}H-NMR: δ 6.02 (1H, s, furyl-4-proton), 2.64 (1H, d), 258 (3H, s, ethylidene Me cis to carbonyl), 2.44 (1H, m), 2.02, 2.27 (6H, s, 2,5-Me), 2.2-0.66 (12H, m); IR ν_{max}/cm^{-1} 1806, 176 / (CO).

Dicyclopropylmethylene-(E)-a-(2,5-dimethyl-3-thienyl)ethylidenesuccinic anhydride **9b**.

This fulgide was prepared in 20% yield by two successive Stobbe condensation of dimethyl

succinate and dicyclopropyl ketone and then 3-acetyl-2,5-dimethylthiophen respectively using the modified procedure previously described by the author [14] yellow crystals, mp 118-120°C (from methanol) (Found: C, 69.23; H, 6.21. $C_{19}H_{20}SO_3$ requires C, 69.48; H, 6.14%); ^{1}H-NMR; 6.52 (1H, s, thienyl-4-H), 3.04 (1H, s, cyclopropyl bridge head proton), 2.63 (3H, s, ethylidene Me cis to carbonyl), 2.40, 2.21 (6H, s, 2,5-Me) 1.21-0.3 (9H, m, cyclopropyl protons); IR ν_{max}/cm^{-1} 1811, 1764 (CO).

Diphenylmethylenesuccinic anhydride **16**

This anhydride was prepared by condensing benzophenone and dimethyl succinate followed by hydrolysis of the resulting half-ester and cyclization of the formed diacid as described for fulgide **9a** and 9b. The product was obtained in 70% yield as yellow crystals; mp 112-114°C (from ethanol) (Found: C, 77.51; H, 4.32 $C_{17}H_{12}O_3$ requires C, 77.27; H, 4.55%); ^{1}H-NMR: δ 7.74-7.17 (10H, m, aromatic protons), 3.74 (2H, s, methylene protons); MS m/z 264 (M, 56%), 220 (11), 192 (100), 191 (67), 165 (22), 115 (15), 92 (64), 91 (93).

Ring opening reactions of fulgides

Preparation of methyl diphenylmethylene (isopropylidene) succinate **4a**

A solution of fulgide **3** (0.5 g, 1.65 mmol) and potassium methoxide (0.2 g, 2.8 mmol) in dry methanol (20 ml) was refluxed for 5 h. Solvent was removed under reduced pressure, ether was added and dilute HCl (10 ml, 10%) was added. The ether layer was separated and washed with water (2x50 ml), dried (MgSO4) and concentrated. The half-ester **4a** was collected on filtration and crystallized from ethanol to give colourless crystals (0.47 g, 93%), mp 140-142°C. (Found: C, 75.21; H, 5.85. $C_{21}H_{20}O_4$ requires C, 75.01; H, 5.95%); ^{1}H-NMR (Table-1).

n-Butyl diphenylmethylene(isopropylidene) succinate **4b**.

A solution of fulgide **3** (1.0 g, 3.3 mmol) and n-butyl alcohol (30 ml) was refluxed in the presence of concentrated HCl (5 ml) for 6 h. The solvent was removed and the resulting half-ester was collected and recrystallized from ethanol to give 4b as white powder (0.86 g, 65%), mp 165-167°C. (Found: C, 75.89; H, 6.67 $C_{24}H_{26}O_4$ requires C, 76.20; H, 6.87%); ^{1}H-NMR (Table-1); m/z 378 (M, 100%), 362 (6), 322 (40), 304 (89), 289 (37), 259 (16), 245 (19), 233 (20), 215 (25), 205 (10), 165 (9), 105 (46), 77 (13).

General proedure of the preparation of compounds **4c-d**

A solution of fulgide 3 (1.0 mmol) and the appropriate amine (1.0 mmol) in dry TFH (100 ml) was stirred for 12 h. The solvent was removed under reduced pressure and the residue was crystallized from ethanol.

3-Diphenylmethylene-4-isopropylidene-4-oxo-4-diethylaminobutanic acid **4c**

The product was obtained in 40% yield as white plates, mp 182-185°C (Found: C, 63.44; H, 6.98; N, 3.55. $C_{24}H_{27}NO_3$ requires C, 63.66; H, 7.16; N, 3.71%); ^{1}H-NMR (Table-1); MS m/z 377 (M, 100%), 348 (18), 333 (8), 304 (16), 272 (19), 215 (20), 186 (15), 167 (20), 148 (39), 105 (32), 100 (35), 72 (45).

3-Diphenylmethylene-4-isopropylidene-4-oxo-4-pipyridinobutanoic acid **4d**

The product was obtained in 65% yield as white crystals, mp 205-207°C (Found: C, 77.34; H, 6.83; N, 3.39. $C_{25}H_{27}NO_3$ requires C, 77.12; H, 6.94; N, 3.60%); ^{1}H-NMR (Table-1); MS m/z 389 (M, 68), 345 (24), 330 (9), 304 (16), 262 (46), 215 (21), 178 (25), 160 (47), 112 (27), 84 (100), 70 (36).

3-Diphenylmethylene-4-isopropylidene-4-oxo-4-(p-tolylamino)butanoic acid **4e**

A solution of fulgide 3 (1.0 g, 3.3 mmol) and p-toluidine (0.35 g, 3.3 mmol) in toluene (50 ml) was refluxed for 6 h., the solution was concentrated and cooled, the precipitated succinamic acid 4e was collected by filtration and recrystallized from ethanol to give colourless crysals (1.1 g, 82% yield), mp 195-197°C (Found: C, 78.72, H, 5.88; N, 3.20. $C_{27}H_{25}NO_3$ requires C, 78.81; H, 6.12; N, 3.40%); ^{1}H-NMR (Table-1).

General procedure for the synthesis of dicyanomethylene derivatives **12a**, **12b** *and* **17**

A solution of fulgide (3 mmol) and malononitrile (3 mmol) in dry THF (20 ml) was stirred at 0°C for 10 minutes under nitrogen atmosphere. Diethyl amine (6 mmol) was added

drop-wise with stirring, after the addition was completed white precipitate started to deposit. The reaction mixture was left stirring for 3 h., then diethyl ehter (25 ml) was added. The white solid formed was filtered and dissolved in dichloromethane (20 ml) and cyclized by stirring for 6 h. with acetyl chloride (5 ml) at room temperature. The solvent was removed and the crude product was chromatographed on silica gel using a 3:7 mixture of ethyl acetate and petroleum ether (40-60) as eluent.

5-Dicyanomethylene-3-(E)-α-(2,5-dimethyl-3-furyl)ethylidene-4-trimethylene-2-norbornylidenetetrahydrofuran-2-one **12a**

Yellow powder (25% yield), mp 180-182°C (Found: C, 74.82; H, 6.10; N, 6.82. $C_{25}H_{24}N_2O_3$ requires C, 74.91; H, 5.99; N, 6.99%); ^{1}H-NMR: δ 5.92 (1H, s, furyl-4-proton), 3.90 (1H, d), 2.43 (3H, s, ethylidene Me cis to carbonyl), 2.34 (1H, m), 1.98, 2.15 (6H, s, 2,5-Me), 2.52-0.74 (12H, m); IR νmax/cm^{-1} 2226 (CN), 1710 (CO).

5-Dicyanomethylene-4-dicyclopropylmethylene-3-(E)-α-(2,5-dimethyl-3-thienyl) ethylidenetetrahydrofuran-2-one **12a**

Pale yellow crystals (10% yield), mp 130-132°C (Found: C, 69.92; H, 5.43; N, 7.58. $C_{22}H_{20}SN_2O_2$ requires C, 70.21; H, 5.31; N, 7.45%); ^{1}H-NMR: δ 6.45 (1H, s, thienyl-4-H), 3.47 (1H, s, cyclopropyl bridgehead proton), 2.52 (3H, s, ethylidene Me cis to carbonyl), 2.36 2.13 (6H, s, 2,5-Me), 1.28-0.35 (9H, m, cyclopropyl protons); ν_{max}/cm^{-1} 2230 (CN), 1701 (CO).

2-Dicyanomethylene-3-diphenylmethyl-2,5-dihydrofuran-5-one **17**

Pale yellow solid (34% yield) mp 120-125°C (Found: C, 77.84; H, 4.21; N, 7.96 $C_{20}H_{12}N_2O_2$ requires C, 77.92; H, 3.90; N, 7.79%): ^{1}H-NMR: δ 7.50-713 (10H,m, aromatic protons), 5.35 (1H, s, methyl protons), 4.15 (1H, s, olefinic protons); IR ν_{max}/cm^{-1} 2227 (CN), 1740 (CO).

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