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Photochemical Dimerization in Solution of Arylacrylonitrile Derivatives

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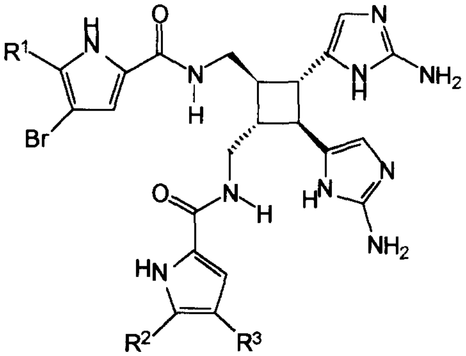
Abstract - The photochemical irradiation of acrylonitrile derivatives bearing either aromatic or heteroaromatic rings as substituents on C-3 gives dimeric products. The reactions were carried out in acetonitrile in the presence of benzophenone as sensitizer. The most abundant dimer showed a structure similar to dimeric compounds isolated in Caribbean sponges showing antimicrobial activity. The regiochemical control in the formation of the dimers can be rationalised considering the overlap of the frontier orbitals involved in the reaction. The stereochemistry can be explained considering the heat of formation of the dimers: the most stable dimers are formed. © 1997 Elsevier Science Ltd.

Some years ago, the isolation of some cyclobutane derivatives **1-3** from Caribbean sponges *Agelas sceptrum* and *Agelas conifera* has been described.[1-3] These compounds were characterised by the presence of two imidazole rings and amide groups. Furthermore, these compounds showed antimicrobial and antibacterial activities.[1,2]



1: $R^1 = R^2 = H$, $R^3 = Br$
2: $R^1 = R^2 = R^3 = H$
3: $R^1 = R^2 = R^3 = Br$

We reported that cyclobutane derivatives can be obtained by irradiation of methyl 3-(2-furyl)acrylate in the presence of benzophenone in acetonitrile.[4-6] Recently, we reported also a theoretical explanation of the photochemical behaviour of furylacrylates on the basis of both the frontier orbitals interaction and the stability of the dimers.

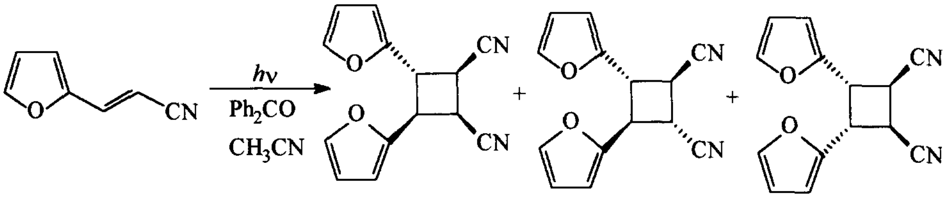
In a project devoted to find and set up a photochemical method for the synthesis of compounds **1-3**, here we want to report our results on the photochemical dimerization of acrylonitrile derivatives. The cyclobutane derivatives thus obtained could represent a model for the synthesis of compounds **1-3**. Furthermore, the results described below can represent a control of our theoretical model for this photochemical reaction. Finally, the photochemical dimerization of aryl and heteroaryl derivatives is not described in literature and the obtaining of these dimers could represent an interesting goal for our described photosensitised dimerization methodology in solution.

Results and Discussion

In this work we used as starting material the acrylonitrile derivatives **4-7**. 3-(2-Furyl)acrylonitrile (**4**), 3-(2-thienyl)acrylonitrile (**5**), and cinnamonitrile (**6**) are commercially available, while 3-(3,4,5-trimethoxyphenyl)acrylonitrile (**7**) can be obtained by using a described aldol condensation between 3,4,5-trimethoxybenzaldehyde and acetonitrile.[7]

The irradiation of **4** in the presence of benzophenone in acetonitrile gave a mixture of three cyclobutane derivatives **8-10** as described in Scheme 1 and Table 1.

Scheme 1



4 **8** **9** **10**

From a synthetic point of view it is noteworthy that the compound obtained in the highest yield (**9**) shows the same stereochemistry of the naturally occurring cyclobutanes **1-3**. The regiochemical behaviour can be explained assuming frontier orbital control of the reaction. We estimated the HOMO and the LUMO energies for the compound **4** by using PM3-RHF-CI semiempirical method and the results are collected in Table 2.[8] In fact, the best interaction occurs between the LSOMO of the excited triplet state and the HOMO of the ground singlet state. Nevertheless, the interaction between the HSOMO of the triplet state and the LUMO of the ground singlet state shows a very similar value. The L and HSOMOs for the triplet state and the HOMO and the LUMO for the ground singlet state of the same molecule are depicted in Figure 1.

Table 1 - Photochemical synthesis of cyclobutanes from acrylonitrile derivatives

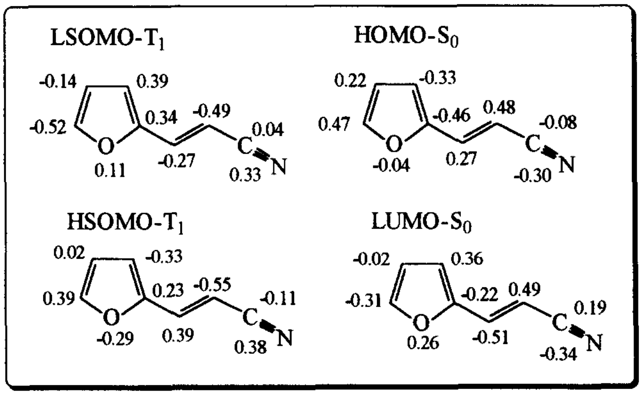
Substrate	Irradiation time (h)	Conversion (%)	Product	Yield (%)[a]
4	48	82	**8**	25
			9	38
			10	18
5	72	12	**11**	34
			12	31
			13	24
6	24	-	-	-
7	72	72	**14**	55
			15	6

a) All the yields refer to isolated chromatographically pure products.

Table 2 - HOMO and LUMO of acrylonitrile derivatives

Compound	Electronic state	HOMO (eV)	LUMO (eV)	LSOMO (eV)	HSOMO (eV)
4	S_0	- 9.017	- 1.046		
	T_1		0.615	- 6.468	- 3.621
5	S_0	- 9.253	- 1.195		
	T_1		- 1.104	- 6.417	- 2.595
7	S_0	- 8.618	- 1.197		
	T_1		0.129	- 6.333	- 3.481

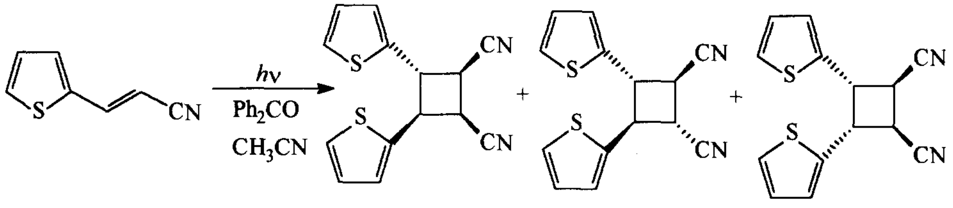
Figure 1 - LSOMO and HSOMO of T_1 and HOMO and LUMO of S_0 of compound **4**.



Therefore, we can see that we have a total superposition between both LSOMO/HOMO and HSOMO/LUMO of the reagents. These data are in agreement with the exclusive formation of head-to-head dimers. The stereochemical behaviour of the dimerization of 3-(2-furyl)acrylonitrile can be explained calculating the heat of formation for all the possible head-to-head dimers. Calculations were performed by using PM3-RHF semiempirical method. The data are collected in Table 3. We can see that the more stable dimers are the obtained ones in agreement with our previous reported results.[6] Furthermore, the different stability between the dimers accounts for the different yields observed. Nevertheless, it is noteworthy that the calculated differences between the dimers are very small. In particular, it is not clear why we obtained the compound **10** (heat of formation 76.74 kcal mol^{-1}) while we did not observe the formation of the dimer showing the heat of formation of 76.90 kcal mol^{-1}.

When the photochemical reaction was performed on 3-(2-thienyl)acrylonitrile (**5**), under the same conditions, we obtained the products described in Scheme 2 and Table 1.

Scheme 2



5 **11** **12** **13**

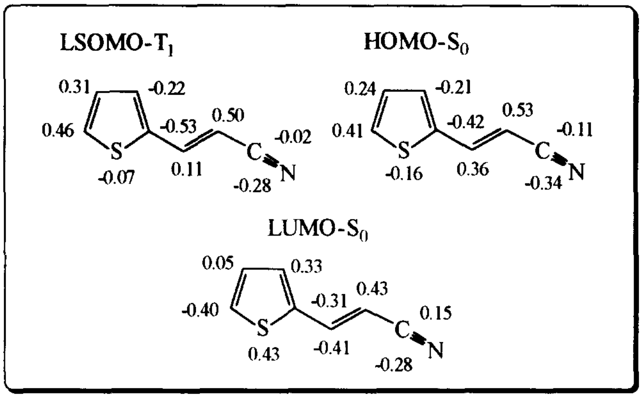
We obtained the same type of products with similar yields. On the contrary, the conversion in this case was very low. In this case the regiochemistry can be explained considering the interactions between both the LSOMO of the triplet state of **5** and the HOMO of the fundamental singlet state of the same molecule and the HSOMO of the triplet state and the LUMO of the fundamental singlet state (Table 2, Figure 2). The best interaction was obtained between the HSOMO of T_1 and LUMO of S_0. However, the HSOMO is not a π orbital and it can not give frontier orbital control.

It is noteworthy that, assuming that the only frontier orbital interaction is between the HSOMO of T_1 and the LUMO of S_0, in this case the gap between these two orbitals is higher than by using compound **4**. This datum is in agreement with the observed lower reactivity of **5** in comparison with **4**.

Also in this case, the obtaining of compounds **11-13** can be explained on the basis of the different stability of all the possible dimers, as reported in Table 3.

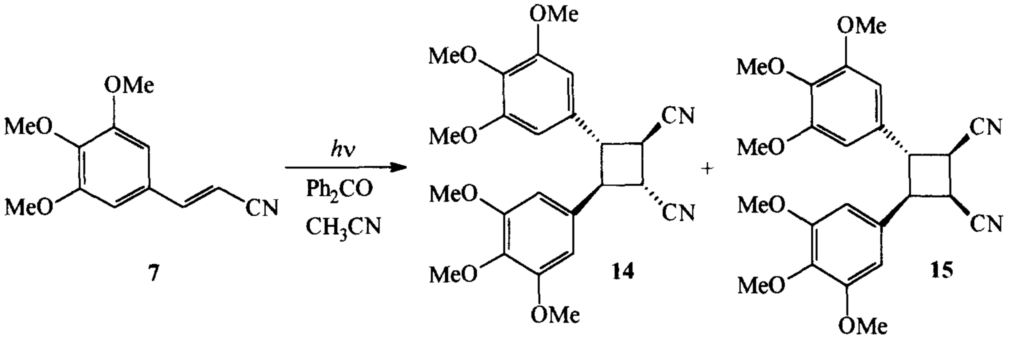
The photochemical irradiation of cinnamonitrile (**6**) in acetonitrile in the presence of benzophenone did not give results. The photochemical behaviour of this substrate is similar to that reported in the case of ethyl cinnamate.[4] Also in this case, in fact, the substrate was recovered unchanged after prolonged reaction times. The reason of this behaviour is not clear. Nevertheless, the irradiation of methoxy substituted cinnamic esters

Figure 2 - Frontier orbitals of compound **5**



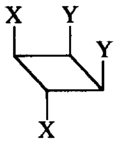
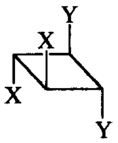
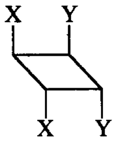
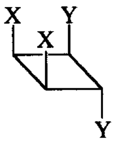
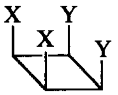
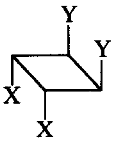
gave the expected reactivity.[9] In our experiments, we used as substrate 3-(3,4,5-trimethoxyphenyl)acrylonitrile (**7**). The irradiation of this substrate under the above described conditions gave a mixture of two dimers (**14** and **15**), corresponding to those obtained in highest yields with **4** and **5** (Scheme 3, Table 1).

Scheme 3



Also in this case the regio and stereochemical behaviour of the substrate can be explained on the basis of the frontier orbital interactions and considering the heat of formation of the dimers. The data reported in Table 2 on the energy of the frontier orbitals showed that both the interactions (LSOMO/HOMO and HSOMO/LUMO) can be possible. In Figure 3 we have reported the atomic coefficients of the frontier orbitals involved. In all the cases we obtained a good overlap between the frontier orbitals, and in all the cases only head-to-head dimers can be obtained.

Table 3 - **Heat** of Formation of all the Head-to-head Dimers of Arylacrylonitrile Derivatives

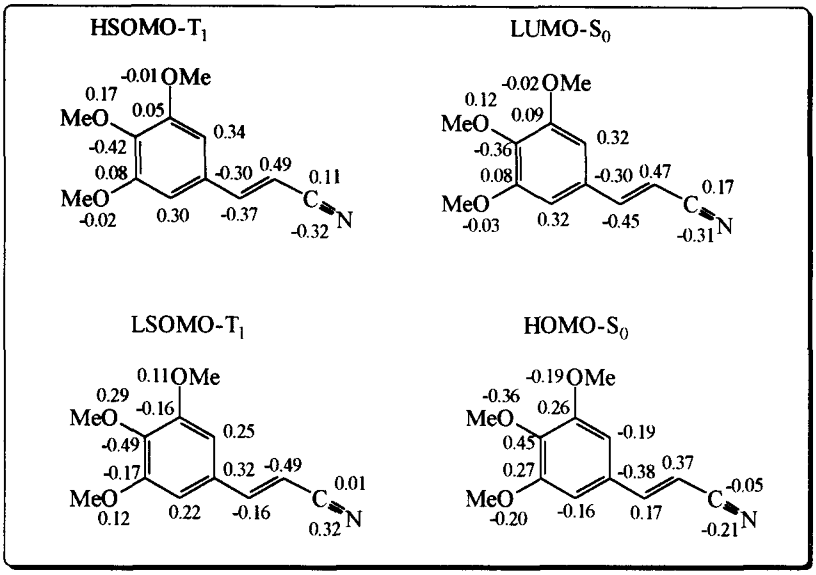
Dimer	Heat of Formation (kcal mol^{-1})		
	Furan[a]	Thiophene[b]	Aryl[c]
	76.58	148.88	-85.14
	73.31	146.48	-90.61
	76.90	149.81	-84.20
	81.77	154.12	-82.25
	85.67	161.82	-75.52
	76.74	148.97	-83.52

a) X = 2-Furyl, Y = CN

b) X = 2-Thienyl, Y = CN

c) X = 3,4,5-Trimethoxyphenyl, Y = CN

Figure 3 - Frontier orbitals of compounds 7.



On the basis of the data collected in Table 3 also the stereochemistry of the reaction can be explained. In fact, the compounds **14** and **15** are the most stable ones between all the possible head-to-head isomers.

In conclusion we have seen that the photochemical dimerization in solution can be used in order to obtain dimers from compounds never dimerized before. We have seen also that the dimerization reaction can be rationalised considering the frontier orbital interactions and the stability of dimers. Finally, this reaction could be useful in order to obtain dimeric vinyl imidazole derivatives with important biological properties. This will be the object of our work in the near future.

Experimental

Mass spectra were obtained with an Hewlett-Packard 5971 mass selective detector on a Hewlett-Packard 5890 gaschromatograph. Gas-chromatographic analyses were obtained on a OV-1 capillary column between 70-250 °C (20 °C/min). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 300 AM instrument. 3-(2-Furyl)acrylonitrile, 3,4,5-trimethoxybenzaldehyde, and benzophenone were obtained by Aldrich. 3-(2-Thienyl)acrylonitrile was obtained by Maybridge Chemical co. Both 3-(2-furyl)acrylonitrile and 3-(2-thienyl)acrylonitrile were distilled under reduced pressure before use.

3-(3,4,5-trimethoxyphenyl)acrylonitrile (**7**). In a 500 ml, three-necked round bottomed flask, equipped with a condenser and a charging funnel, were dissolved 3.3 g of KOH in 200 ml of acetonitrile. The funnel was charged with 9.8 g of 3,4,5-trimethoxybenzaldehyde in 50 ml of acetonitrile, and the system was brought under reflux with a stream of nitrogen. The aldehyde was added in 1 - 2 min and, after 15 min, the mixture was poured in a 1l beaker with cracked ice. Extraction with Et_2O yielded 3.2 g of crude product which was purified on silica gel (eluent petroleum ether - dichloromethane - ethyl acetate 6 :3 :1) to provide 2.4 g of 3-(3,4,5-trimethoxyphenyl)acrylonitrile as a 40:60 *cis-trans* mixture. ^1H NMR ($CDCl_3$) δ : *cis* : 3.87 (3 H, s), 3.88 (6 H, s), 5.38 (1 H, d, J = 12 Hz), 7.03 (1 H, d, J = 12 Hz), 7.13 (2 H, s) ; *trans* : 3.88 (6 H, s), 3.90 (3 H, s), 5.78 (1 H, d, J = 16.6 Hz), 6.66 (2 H, s), 7.31 (1 H, d, J = 16.6 Hz).

General procedure for photodimerization. The nitrile (3 g) and benzophenone (600 mg) were dissolved in acetonitrile (90 ml) and degassed for 1 h with a stream of nitrogen. The solution was then irradiated with a 125 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water jacket. After three days (two days in the case of 3-(2-furyl)acrylonitrile) the solvent was evaporated and the crude product was chromatographed on SiO_2 (eluent petroleum ether - toluene - dichloromethane - ethyl acetate 7 :1 :1.5 :0.5, petroleum ether - ethyl acetate 6 :4 in the case of compound **7**). The analyses of the ^1H NMR spectra of compounds **9**, **10**, **12**, **13**, and **14** is reported in Table 4 on the basis of the Ref. 10. In particular, we obtained from the spectra the N, L, K, and M parameters. These values were used to calculate the coupling constants J (J_{AB} in a AA'BB' system), J' ($J_{AB'}$), J_A ($J_{AA'}$), and J_B ($J_{BB'}$), on the basis of the following equations:

$$K = (J_A + J_B)$$

$$M = (J_A - J_B)$$

$$N = (J + J')$$

$$L = (J - J')$$

Table 4 - Analysis of the AA'BB' part of the ^1H NMR spectra of dimeric compounds

Compound	N	L	K	M	J	J'	J_A	J_B
9	6.2	1.6	18	0	3.9	2.3	9	9
10	9.7	2.5	12	0	6.1	3.6	6	6
12	6.0	2.0	18	0	4.0	2.0	9	9
13	9.0	2.5	12	0	5.7	3.2	6	6
14	9.0	3.5	18	0	5.8	2.3	9	9

The obtained values for J are in agreement with a *trans* relationship between the A and B part of system, while the values of J_A and J_b are in agreement with a *trans* relationship between A and A' and B and B', respectively, when the value is 9 Hz and in agreement with a *cis* relationship when the value is 6 Hz.

t-3,c-4-Di-(2-furyl)cyclobutane-r-1,c-2-dicarbonitrile (**8**). M. p. 139 – 139 °C (from heptane/toluene). ^{1}H NMR ($CDCl_3$) δ : 3.67 (1 H, dd, J_1 = 9.7 Hz, J_2 = 8.4 Hz), 3.86 (1 H, dd, J_1 = J_2 = 8.4 Hz), 4.13 (1 H, dd, J_1 = 10.4 Hz, J_2 = 8.4 Hz), 4.38 (1 H, dd, J_1 = J_2 = 10.4 Hz), 6.31 (1 H, m), 6.35 (1 H, m), 6.40 (1 H, m), 6.43 (1 H, m), 7.42 (1 H, d, J = 1.5 Hz), and 7.45 ppm (1 H, d, J = 1.4 Hz) ; ^{13}C NMR ($CDCl_3$) δ : 28.99, 32.11, 39.63, 42.63, 108.93, 109.23, 110.80, 110.90, 115.65, 116.16, 143.31, 143.48, 146.72, and 148.97 ppm. Elemental Analysis: Found: C, 71.2; H, 6.6; N, 10.3. Calc for $C_{14}H_{10}N_2O_2$: C, 71.09; H, 6.71; N, 10.36%.

c-3,t-4-Di-(2-furyl)cyclobutane-r-1,t-2-dicarbonitrile (**9**). M. p. 64 –66 °C (from hexanes/chloroform). ^{1}H NMR ($CDCl_3$) δ : 4.03 (2 H, m), 4.37 (2 H, m), 6.01 (2 H, d, J = 3.2 Hz), 6.26 (2 H, dd, J_1 = 3.2 Hz, J_2 = 1.8 Hz), and 7.29 ppm (2 H, d, J = 1.5 Hz) ; ^{13}C NMR ($CDCl_3$) δ : 29.78, 41.53, 108.95, 110.73, 116.92, 142.73, and 148.48 ppm. Elemental Analysis: Found: C, 71.1; H, 6.8; N, 10.4. Calc for $C_{14}H_{10}N_2O_2$: C, 71.09; H, 6.71; N, 10.36%.

t-3,t-4-Di-(2-furyl)cyclobutane-r-1,c-2-dicarbonitrile (**10**). M. p. 127 – 128 °C (from hexanes/chloroform). ^{1}H NMR ($CDCl_3$) δ : 3.58 (2 H, m), 4.01 (2 H, m), 6.25 (2 H, m), 6.35 (2 H, m), and 7.45 ppm (2 H, d, J = 1.4 Hz) ; ^{13}C NMR ($CDCl_3$) δ : 29.69, 42.69, 109.00, 110.89, 117.20, 143.49, and 148.92 ppm. Elemental Analysis: Found: C, 71.2; H, 6.8; N, 10.3. Calc for $C_{14}H_{10}N_2O_2$: C, 71.09; H, 6.71; N, 10.36%.

t-3,c-4-Di-(2-thienyl)cyclobutane-r-1,c-2-dicarbonitrile (**11**). M. p. 159 – 160 °C (from heptane/toluene). ^{1}H NMR ($CDCl_3$) δ : 3.47 (1 H, dd, J_1 = 8.1 Hz, J_2 = 10.4 Hz), 3.91 (1 H, dd, J_1 = J_2 = 8.4 Hz), 4.13 (1 H, dd, J_1 = 10.4 Hz, J_2 = 8.4 Hz), 4.54 (1 H, dd, J_1 = J_2 = 10.4 Hz), 7.01 (2 H, m), 7.07 (1 H, m), 7.19 (1 H, m), and 7.32 ppm (2 H, m). ^{13}C NMR (DMSO-d_6) δ: 30.37, 33.80, 43.25, 45.39, 117.14, 125.94, 126.11, 126.57, 127.23. 138.49, and 140.43 ppm. Elemental Analysis: Found: C, 63.6; H, 6.2; N, 9.2; S, 21.1. Calc for $C_{14}H_{10}N_2S_2$: C, 63.54; H, 6.00; N, 9.26; S, 21.20%.

c-3,t-4-Di-(2-thienyl)cyclobutane-r-1,t-2-dicarbonitrile (**12**). M. p. 78 –79 °C (from heptane/toluene). ^{1}H NMR ($CDCl_3$) δ : 3.97 (2 H, m), 4.66 (2 H, m), 6.78 (2 H, m), 6.92 (2 H, m), and 7.21 ppm (2 H, m). ^{13}C

NMR ($CDCl_3$) δ: 31.77, 44.30, 116.31, 126.07, 126.32, 126.37, and 137.14 ppm. Elemental Analysis: Found: C, 63.7; H, 6.1; N, 9.1; S, 21.2. Calc for $C_{14}H_{10}N_2S_2$: C, 63.54; H, 6.00; N, 9.26; S, 21.20%.

t-3,t-4-Di-(2-thienyl)cyclobutane-r-1,c-2-dicarbonitrile (**13**). Viscous oil. ^{1}H NMR ($CDCl_3$) δ : 3.42 (2 H, m), 4.07 (2 H, m), 7.02 (4 H, m), and 7.32 ppm (2 H, m). ^{13}C NMR ($CDCl_3$) δ: 32.37, 47.88, 116.88, 125.84, 125.86, 127.53, and 139.56 ppm. Elemental Analysis: Found: C, 63.5; H, 6.0; N, 9.1; S, 21.3. Calc for $C_{14}H_{10}N_2S_2$: C, 63.54; H, 6.00; N, 9.26; S, 21.20%.

c-3,t-4-Di-(3,4,5-trimethoxyphenyl)cyclobutane-r-1,t-2-dicarbonitrile (**14**). M. p. 189 – 191 °C (from methanol). ^{1}H NMR ($CDCl_3$) δ : 3.68 (12 H, s), 3.77 (6 H, s), 3.87 (2 H, m), 4.41 (2 H, m), and 6.18 ppm (4 H, s). ^{13}C NMR ($CDCl_3$) δ: 29.84, 47.99, 56.26, 60.71, 105.33, 117.67, 130.20, 138.15, and 153.34 ppm. Elemental Analysis: Found: C, 65.6; H, 6.0; N, 6.5. Calc for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39%.

t-3,c-4-Di-(3,4,5-trimethoxyphenyl)cyclobutane-r-1,c-2-dicarbonitrile (**15**). M. p. 161 – 163 °C (from methanol). ^{1} H NMR ($CDCl_3$) δ : 3.69 (12 H, s), 3.77 (3 H, s), 3.79 (3 H, s), 3.87 (1 H, dd, J = 9.8 Hz), 3.99 (1 H, dd, $J_1 = J_2$ = 7.6 Hz), 4.27 (1 H, dd, $J_1 = J_2$ = 9.8 Hz), 4.35 (1 H, dd, $J_1 = J_2$ = 7.6 Hz), 6.13 (2 H, s), and 6.29 ppm (2 H, s). ^{13}C NMR ($CDCl_3$) δ: 29.68, 31.07, 46.74, 56.20, 60.71, 104.55, 106.91, 116.42, 118.01, 128.99, 130.79, 137.94, 138.22, 153.15, and 153.37 ppm. Elemental Analysis: Found: C, 65.8; H, 6.1; N, 6.3. Calc for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39%.

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