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PHOTOREACTION OF BENZENECARBOTHIOAMIDE WITH OLEFINS. SYNTHESES OF ISOTHIAZOLE DERIVATIVES AND PHENONES[1]

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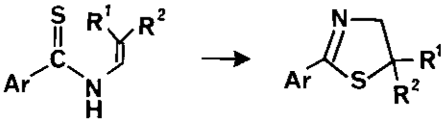
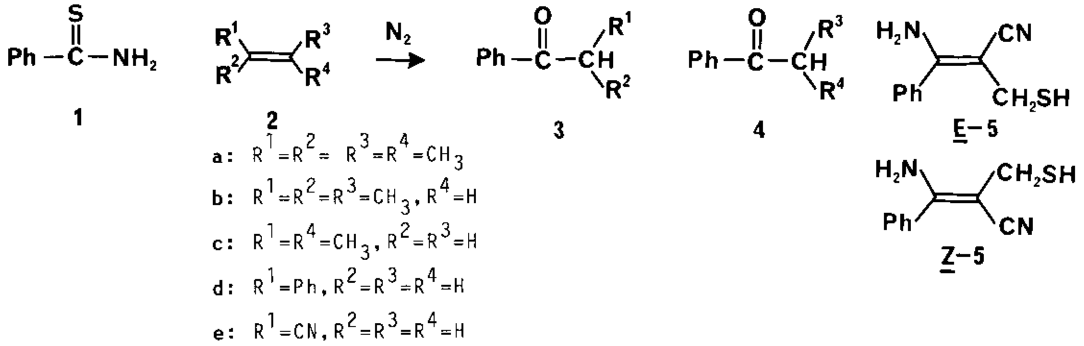
Abstract——Photoreaction of benzenecarbothioamide **(1)** in the presence of olefins gave isothiazole derivatives **(10, 12, and 13)** and 3,5-diphenyl-1,2,4-thiadiazole **(11)** under aerobic conditions, whereas under nitrogen atmosphere gave phenones **(3 and 4)**.

Although the photochemistry of thione has been extensively studied,[2] few reports have dealt with the photochemical properties of thioamides: namely, thiobenzanilides[3] and 4-thiouracils[4] have been major subjects in literature, and little had been known of photoreactions of arenecarbothioamides. As a logical extension of our photochemical studies of the nitrogen-carbonyl systems,[5] we have already reported on the intermolecular photoreaction of arenecarbothioamides with unsaturated systems.[6] Recently, Couture et al. have reported intramolecular photoreactions of thienamide (Scheme 1).[7] The present report is concerned with full details of further research on the photoreaction of benzenecarbothioamide with unsaturated systems.



Scheme 1

Irradiation of benzenecarbothioamide with olefins was carried out in benzene using a 1 kW high-pressure mercury lamp through a Pyrex filter. The results under nitrogen atmosphere (in the absence of oxygen) are listed in Table I. Irradiation of benzenecarbothioamide **(1)** and five equivalents of 2,3-dimetyl-2-butene **(2a)** for 20 h gave exclusively isobutyrophenone **(3a)** in 18% yield (Scheme 2). Similarly, in the case of the presence of 2-methyl-2-butene **(2b)** or trans-2-butene **(2c)**, the photoreactions gave isobutyrophenone **(3a)** and propiophenone **(3c)** in 12 and 16% yields,



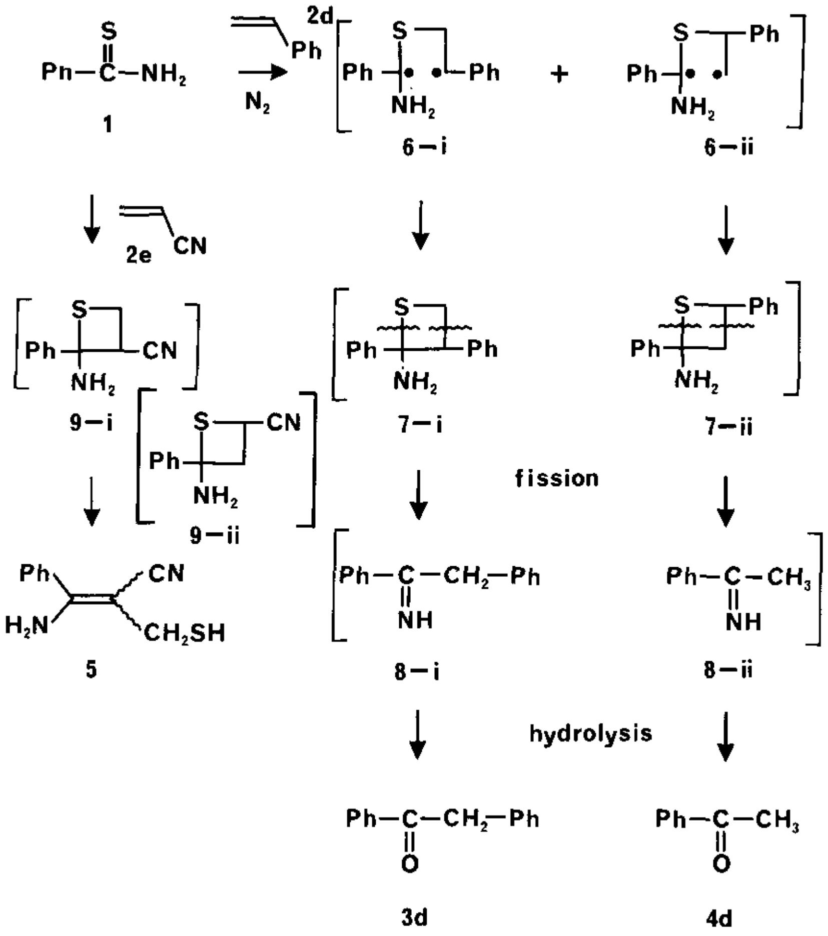
a: $R^1=R^2=R^3=R^4=CH_3$
b: $R^1=R^2=R^3=CH_3, R^4=H$
c: $R^1=R^4=CH_3, R^2=R^3=H$
d: $R^1=Ph, R^2=R^3=R^4=H$
e: $R^1=CN, R^2=R^3=R^4=H$

Scheme 2

Table I. Photoreaction of **1** in the Presence of Olefins (**2**) Under Nitrogen Atmosphere

Olefin	Mole ratio 2/1	Irradiation time (h)	Yield (%) 3	4	5	Recovery 1
2a	5	20	18			64
	30	2	76			16
2b	5	20	12			58
2c	5	20	16			68
2d	30	4	71	7		
2e	30	8			82	

respectively. In each case, benzenecarbothioamide **1** was recovered unchanged in 58-68% yields even after prolonged irradiation for 20 h. Further, taking into account that olefins are volatile, 30 equivalents of **2a** toward **1** were used. The yield of **3a** increased up to 76% upon short irradiation for 2 h. With aromatic conjugated olefin such as styrene (**2d**), two phenones, deoxybenzoine (**3d**) and acetophenone (**4d**), were obtained in a 10:1 ratio. However in the case of acrylonitrile (**2e**) having an electron withdrawing group, **1** gave efficiently amino thiol compound (**5**), as a mixture of two geometrical isomers which are inseparable, and none of phenones and other products were isolated. Thus, by use of a large excess of olefins (30 equivalents), benzenecarbothioamide **1**, in the absence of oxygen, underwent efficiently the Paterno-Büchi type reaction leading ultimately to phenones **3**, **4**, or **5**. The formation of **3**, **4**, and **5** may be explained as illustrated in Scheme 3. For example **3d** and **4d** arise from the initially formed thietanes (**7-i** and **7-ii**) followed by subsequent photochemical fission of the thietane rings, and then by hydrolysis of generated imines (**8-i** and **8-ii**) during its workup such as chromatography. The thietane formation may be explained in terms of intermediary biradicals (**6-i** and **6-ii**) in parallel to the photoreactions of thioimide systems.[8] The preferential formation of **3d** seems to reflect the stability of the generated biradical (**6-i**), which should be more stable than **6-ii**. For the formation of **5**, only an intermediary thietane (**9-i**) would be postulated regioselectively, leading to **5**, which has a favorable olefin system conjugated both with nitrile and a phenyl group, by photochemical

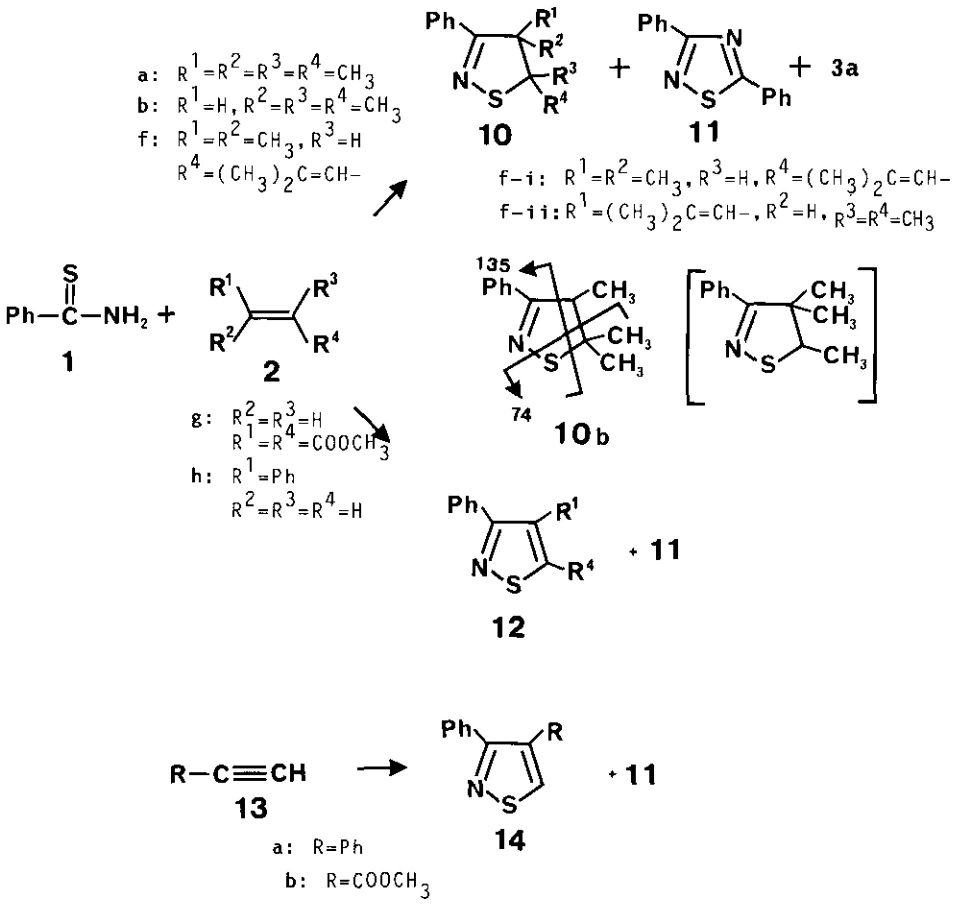


Scheme 3

fission of S-C bond at a benzylic position. Such a fission of thietane ring was discussed in the photoreaction of 4-thiouracil with acrylonitrile.[4b]

The structures of the products **3a**, **3c**, **3d**, and **4d** were assigned on the basis of the spectral and physical data which are reported.[9] The structure of **5** was also determined on the basis of the spectral data. The mass spectrum (ms) of **5** showed a molecular ion peak at m/z 190, which corresponds to an adduct of **1** with **2e**. In the infrared (ir) spectrum, two absorptions due to a nitrile group appeared at 2380 and 2500 cm^{-1}, suggesting existence of two geometrical isomers. The proton nuclear magnetic resonance (^{1}H-nmr) spectrum of **5** also showed to be a 3:2 mixture of two geometrical isomers (E-**5** and Z-**5**); 1.70, 1.80 (1H, t, J=6 Hz, SH), 2.15, 2.35 (2H, d, J=6 Hz, CH_2-SH), 4.75, 4.90 (2H, br s, NH_2), 7.2-7.5 (5H, m, aromatic H). Thus, each signal appeared as a pair of one except for signal due to aromatic protons.

In contrast to the photoreaction under nitrogen atmosphere, irradiation of **1** and **2a**, under aerobic conditions (in the presence of oxygen) for 20 h, gave three products, 3-phenyltetramethyliso-



Scheme 4

Table II. Photoreaction of 1 in the Presence of Olefin (2) or Acetylene (13) Derivatives Under Aerobic Conditions.

Olefin	Mole ratio 2,13/1	Irradiation time (h)	Yield (%) 10	11	12 or 15	3a
2a	5	20	48	22		8
	30	1	52			34
2b	5	20	38	16		6
2f	30	20	48	16		18
2g	5	20		46	18	
2h	5	20		31	16	
13a	2	20		18	22	
13b	20	2		42	26	

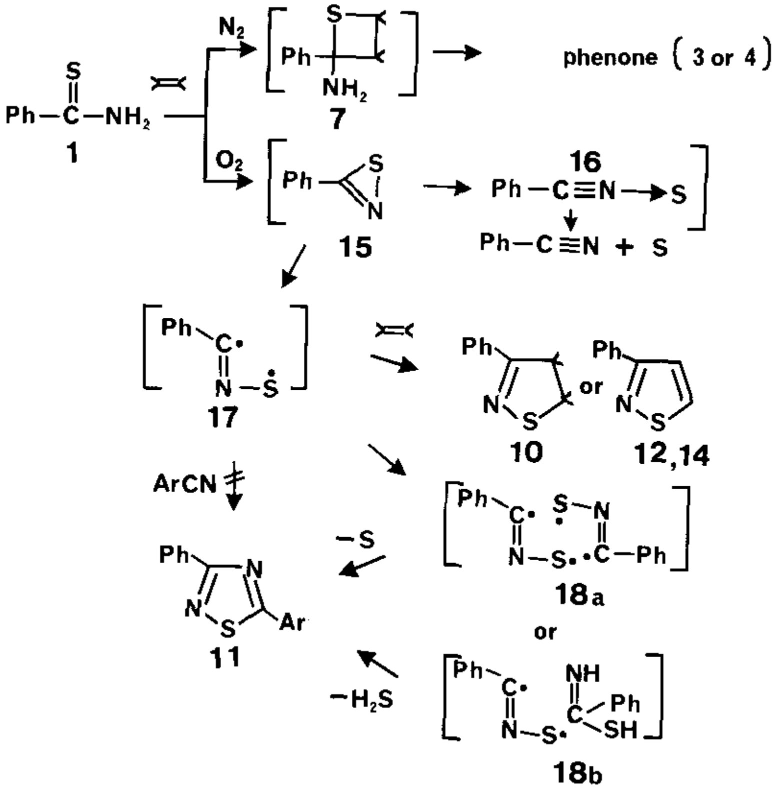
thiazoline (**10a**), 3,5-diphenyl-1,2,4-thiadiazole (**11**), and isobutyrophenone **3a** in 48, 22, and 8% yields, respectively (Scheme 4 and Table II). Compound **11** has been obtained in the absence of olefin under similar conditions as reported previously.[10] Further, in the presence of 30 equivalents of **2a**, on irradiation for 1 h, **1** gave **10a** and **3a** in a similar manner as described above, and the yield for **3a** increased up to 34% but none of thiadiazole was obtained. This suggested that the formation of **11** is slower than those of other products such as **10a** and the corresponding thietane leading to **3a**. The structure of **10a** was determined on the basis of the spectral data. The mass spectrum of **10a** showed the molecular ion peak at m/z 219, which corresponds to the loss of two hydrogens from the molecular weight of an adduct of **1** with **2a**. The ir spectrum indicated a band due to C=N double bond at 1680 cm^{-1}. In the ^{1}H-nmr spectrum, peaks due to four methyl groups appeared at 1.20 (6H, sx2) and 1.30 (6H, sx2) ppm. The ^{13}C-nmr spectrum also supported the presence of four methyl groups (24.8 ppm, qx2 and 18.8 ppm, qx2), and showed three singlet at 55.8, 62.1, and 174.8 ppm, suggesting the presence of two quaternary carbons and a carbon of the C=N double bond, respectively. In addition, in order to investigate the regioselectivity for isothiazoline formation, unsymmetrically substituted olefin **(2b)** was irradiated with **1**. Three products, a single regioisomer **(10b)**, thiadiazole **11**, and **3a** were obtained in the same manner as the product distribution in the case of **2a**. The structure of **10b** was determined on the basis of spectral data. The mass spectrum of **10b** showed the molecular ion peak at m/z 205 and fragment peaks at m/z 135, 102, 74, 69 (selected data). These fragmentations are illustrated in Scheme 4, in which the fragment peak with m/z 74 is due to elimination of $S\text{-}C(CH_3)_2$ from the molecular ion, indicating that gem dimethyl group is attached to the carbon adjacent to sulfur in the isothiazoline ring. The observation of this peak was used to discriminate each of two regioisomers. The ^{1}H-nmr spectrum also supported the structure of **10b**, in which a methine proton resonated at 1.60 ppm as a quartet with the coupling constant of J=7 Hz. Similarly, photolysis of a mixture of conjugated diene (**2f**; 30 equivalents) and **1** gave also isothiazoline **(10f)**, **11**, and **3a**. The resulting isothiazoline was a 2:1 mixture of two inseparable regioisomers (**10f-i** and **10f-ii**) by means of ^{1}H-nmr spectroscopy.

In the case of olefins such as **2g**, **h**, which have a hydrogen both at the olefinic carbons (C_1 and C_2), isothiazole **(12)** and **11** were obtained in moderate yields. The isothiazoles **(12g-j)** seem to arise from the initially formed isothiazolines, which are easily oxidized. With styrene **(2h)**, a single regioisomeric isothiazole **(12h)** was obtained together with **11**. Acetylene derivatives (**13a** and **13b**) which have a triple bond also gave, in each case, regioselectively 4-substituted isothiazoles (**14a=12h** and **14b**, respectively).

The structure of **12h** (**=14a**) was assigned on the basis of the ^{1}H-nmr spectrum. A singlet appeared at 8.50 ppm, indicating the presence of one aromatic proton, whose chemical shift value is very close to that (8.53 ppm) of C_5-proton on the isothiazole ring in the reported 3,4-diphenylisothiazole, whereas the chemical shift of C_4-proton in the 3,5-diphenylisothiazole was reported to be 7.76 ppm.[11] Thus, two regioisomers, 4-unsubstituted and 5-unsubstituted, could be easily discriminated from each other by means of ^{1}H-nmr spectroscopy.

On the other hand, with aliphatic thioamide such as thioacetamide in the presence of **2a** under aerobic conditions, none of products were obtained, and thioacetamide was recovered unchanged. Also, irradiation of N-alkyl thioamide such as N-methylbenzenecarbothioamide was carried out in the presence of **2a** under similar conditions, but N-methylbenzenecabothioamide was quantitatively recovered unchanged. Thus, in the photoreaction of thioamide, both a primary amino group (NH_2) *and an aromatic ring attached to a thiocarbonyl* as seen in the structure of 1 seem to be essential for the formations of isothiazoline and thiadiazole.

In general, nitrile sulfide is believed to undergo the cycloaddition to unsaturated systems leading to isothiazoles and thiadiazole.[12] The formation of nitrile and sulfur, by-products, is common feature of nitrile sulfide chemistry and is attributed to fragmentation competing with 1,3-dipolar cycloaddition to unsaturated systems.[12] In this experiment, extrusion of *sulfur by irradiation* of thioamides suggests the generation of nitrile sulfide **(16)** as an intermediate which decomposed into nitrile and sulfur. In an attempt to trap an expected nitrile sulfide, crossed photochemical reaction between **1** and p-tolunitrile[13] was examined, but none of crossed products were found in the reaction mixture.



Scheme 5

Thus, although evidence for involvement of nitrile sulfide could not be obtained, possibility of its generation still remains. On the other hand, a generation of phenylthiazirine (**15**) as an intermediate, probably by oxidation of **1**, seems to be likely in the aerobic photoreaction of benzenecarbothioamide although none of the spectroscopic and chemical evidences are so far obtained. The generation of phenylthiazirine **15** was suggested by the isolation of a single regioisomer **14** as seen in the photoreaction of **1** with **13**, since generated nitrile sulfide may undergo cycloaddition with unsymmetrical acetylene derivatives such as **13** to give two regioisomers, 4- and 5-substituted isothiazoles. In fact, nitrile sulfide generated by several routes, has given two regioisomeric isothiazole, 4- and 5-substituted, in 0.6-2.3 : 1.0 ratios upon reaction with unsymmetrical acetylenes, thermally or photochemically.[14]

From above results plausible pathways for photolysis of benzenecarbothioamide are outlined in Scheme 5. Under aerobic conditions, involvement of thiazirine **15** was suggested in competition with formation of thietane (**7**). The generated thiazirine **15** may produce a biradical (**17**) by fission of C-S bond, undergoing cycloaddition with olefins to give isothiazolines (**10**) or isothiazoles (**12**, **14**). In the absence of olefins, thiazirine **15** seems to produce thiadiazole (**11**) by dimerization (**18a**) or addition of **1** (**18b**). Thus, it is noteworthy that in the presence of olefins under nitrogen atmosphere, thietane formation of thioamide was observed, whereas under aerobic conditions different oxidative pathway appears leading to isothiazolines or isothiazoles. These results illustrate examples of the marked differences in the photochemical behavior of arenecarbothioamides and arenecarboamides, the latter being incapable of performing these transformations. In addition, these photoreactions may provide, by using a variety of olefins or acetylenes, a simple route to the synthesis of certain sulfur-containing nitrogen-heterocycles, which would serve as potential candidates for antimicrobial and other biologically active agents.[15]

EXPERIMENTAL

All melting points were determined on Yamato melting point apparatus (model MP-21) and were uncorrected. Infrared (ir) spectra were recorded on a JASCO A-102 spectrophotometer. Nmr spectra were taken on a JEOL JNM-FX-90Q spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS (0.0ppm) as an internal standard. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra (ms) were obtained on a JEOL JMS-QH-100 gas chromatograph-mass spectrometer. Preparative irradiations were conducted by using a 1 kW high-pressure mercury lamp (Eikosha EHB-W-1000) through a Pyrex filter at room temperature.

The irradiation of the solutions was performed under conditions of a stream of nitrogen at the bottom of outer jacket (nitrogen atmosphere) or without a stream of nitrogen (aerobic conditions). Column chromatography was conducted using silica gel (Merck, Kieselgel 60, 70-230 mesh).

Irradiation of **1** in the presence of **2** or **13**: General Procedure

A solution of **1** (0.735g 5mmol) and **2a** (10.5g, 25mmol) in benzene (500ml) was irradiated. The solvent was removed in vacuo and the residue was chromatographed on silica gel using a mixture of benzene-n-hexane (1:1 ; v/v) (Tables III, IV). The physical and spectral data for photoproducts **3**, **4**, **12**, and **14** were identical with those of authentic samples.[9]

Table III. Photoproducts

Photoproduct	Appearance	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	S
5	Colorless oil		$C_{10}H_{10}N_2S$	63.16	5.26	14.74	16.84
				(63.40	5.33	14.78	16 69)
10a	Colorless plates	42-43	$C_{13}H_{17}NS$	71.18	7.18	6.39	14.16
				(70.98	7.22	6.45	14.28)
10b	Colorless oil		$C_{12}H_{15}NS$	70.20	7.36	6.82	15.62
				(70.28	7.41	6.66	15.78)
10f	Colorless oil		$C_{15}H_{19}N_2S$	73.47	7.76	5.71	13.06
				(73.59	7.79	5.83	13.25)

Table IV. Spectral Data for Photoproducts

Compound	Ir (cm^{-1})	Ms (m/z)	^{1}H-nmr (CDCl$_3$) δ	^{13}C-nmr (CDCl$_3$) δ
5	3450 3350 3200 2500	190	1.70(1H,t,J=6Hz,-SH), 2.15(2H,d,J=6Hz,-CH$_2$), 4.75(2H, br s,NH$_2$), 7.2-7.5(4H,m,aromatic H).	23.7(t), 77.4(s), 119.8(s), 127.2(dx2), 128.4(dx2), 129.8(d), 133.6(s), 158.5(s)
	2380 1620		1.80(1H,d,J=6Hz,-SH), 2.35(2H,d,J=6Hz,-CH$_2$), 4.90(2H, br s ,NH$_2$), 7.2-7.5(4H,m,aromatic H).	23.0(t), 77.1(s), 122.3(s), 127.5(dx2), 128.1(dx2), 130.0(d), 135.1(s), 158.0(s),
10a	1680	219	1.20(6H,s,Mex2), 1.30(6H,s,Mex2), 7.2-7.6 (5H,m,aromatic H).	18.8(qx2), 24.8(qx2), 55.8(s), 62.1(s), 127.7(dx2), 128.5(dx2),128.6(dx2), 135.8 (s), 174.8(s).
10b	1680	205	1.25(3H,s,Me), 1.30(3H,d,J=7Hz,Me), 1.35 (3H,s,Me), 1.60(1H,q,J=7Hz,CH), 7.2-7.7(5H,m,aromatic H).	13.2(q), 17.7(q), 24.4(q), 55.8(s), 56.8(d), 127.4(dx2), 128.1(dx2), 129.1(d), 135.5 (s), 174.4(s).
10f	1680	245	1.15(3H,s,Me), 1.35(3H,s,Me), 1.60(6H,s, Mex2), 3.40(1H,d,J=9Hz), 5.20(1H,d,J=9Hz), 7.0-7.7(5H,m,aromatic H).	
			1.55(3H,s,Me), 1.65(3H,s,Me), 1.70(6H,s, Mex2), 2.60(1H,d,J=9Hz), 5.20(1H,d,J=9Hz), 7.0-7.7(5H,m,aromatic H).	

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