Reactivity Studies of Thiophosgene and its Halo Versions towards Diazo Derivatives

Sudershan R. Gondi *

Department of Chemistry, Southern Methodist University, 3215 Daniel Avenue, Dallas, Texas 75275-0314, USA

Abstract:

The reactions of thiophosgene with diazo derivatives gives dichloro-alkene derivatives and cyclized, 1,2,3-thiadiazoles respectively. The product formation is mainly depending on substitutions on diazo substrates. When its halo versions, $CSBr_2$ and in combination with bromide ion, $CSBr_2$ less reactive than bromide ion with disubstituted diazo, give gem-dihalo derivatives whereas more reactive with mono substituted diazo to gives 1,2,3-thiadiazoles. In case CSI_2 irrespective of substitution on diazo, iodide ion is more reactive then CSI_2 was observed.

Key words:

Diazo acetate, Thiophosgene, gem-Dihalo, Diazirine, 1,2,3-Thiadiazoles.

Introduction:

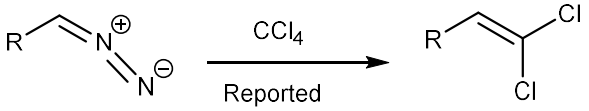
Synthesis of tetra substituted alkenes by using thiocarbonyl and diazo were reported in the literature[1-2]. We are particularly interest, the combination of thiophosgene with diazo derivatives, the compounds obtained by these combinations are thioether[3], thiazolines[4-

[5] dihalo alkene[6], thiocarbonyl chlorides[7], thioisocyate[8] and thiourea[9]. Dihalo alkene also reported by using CCl_4 under anhydrous conditions[10].

Present work:

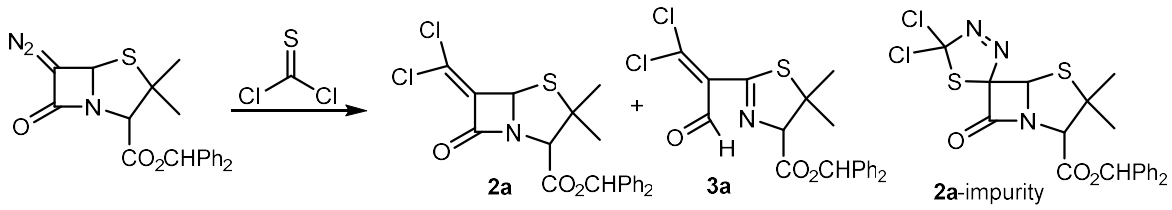
We are interested in the synthesis of dihalo alkenes because it is usefulness for converting into active intermediates[11-13] by using thiophosgene and its halo versions ($CSBr_2$ or CSI_2). To test this, we treated various substrates

Scheme-1



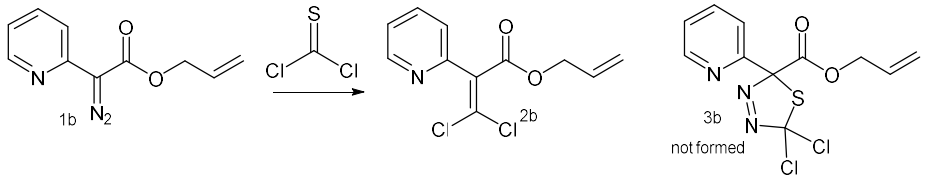
Frist when thiophosgene was treated with **1a** disubstituted diazo[14], we obtained dichloro alkene **2a** as major product along with impurities, and its beta lactam amide bond cleaved product **3a** as minor product. The 3**a** is obtained due the C_5=N bond formation followed by amide bond cleavage. The aldehyde peak in NMR Is consistent with predicted values. in FT-IR shows Isothiocyanate peak at 2060 cm^{-1}, which can be formed by **:**S-C=N enolization[15] The mass m/s shows 447.2 peaks. (scheme-2)

Scheme-2



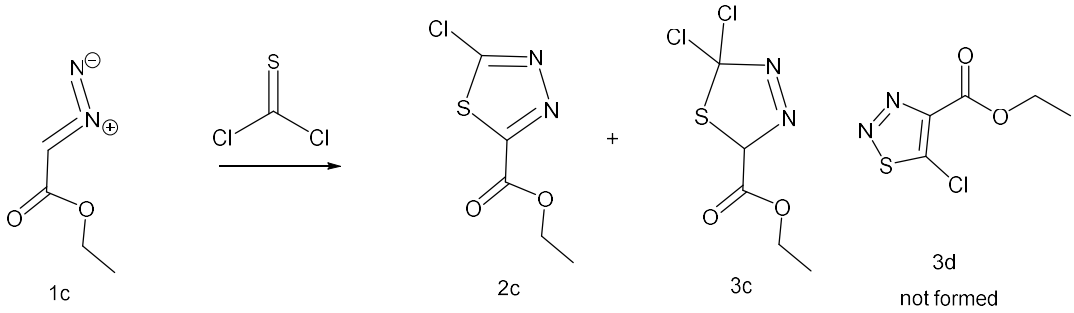
On repeating the reaction with pyridine diazo **1b**, we isolated a product **2b** it contains, the C13-NMR values consistent with product and the characteristics diazo peak in FTIR shows at 2240 cm^{-1} is absent in product **3a**. The formation of **3b** is rules out based on C13-NMR, where gem-dichloro peaks shows at 95 ppm. (Scheme-3)

Scheme-3



After getting disubstituted diazo results, now treated with mono substituted diazo derivatives, ethyl diazo acetate **1c** with thiophosgene. Isolated ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate **2c**, as a major one along with minor dichloro **3c**, where the dichloro bearing carbon shows at 5.2 ppm in Proton-NMR and 103 ppm in carbon NMR spectra (scheme-4). The characteristic peak of chloro bearing carbon at 157.6 ppm in carbon NMR confirmed the 1,3,4 thiadiazole ring. It means **3c** is formed first, on 1,4 elimination of HCl gives **2c**. In reported method, 1,3,4-thaizdiazole-2-carboxylate were isolated as single by using thiolate[16]. or by using thiophosgene[17] gives mixture or products, ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate **2c** along with ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate **3d**.

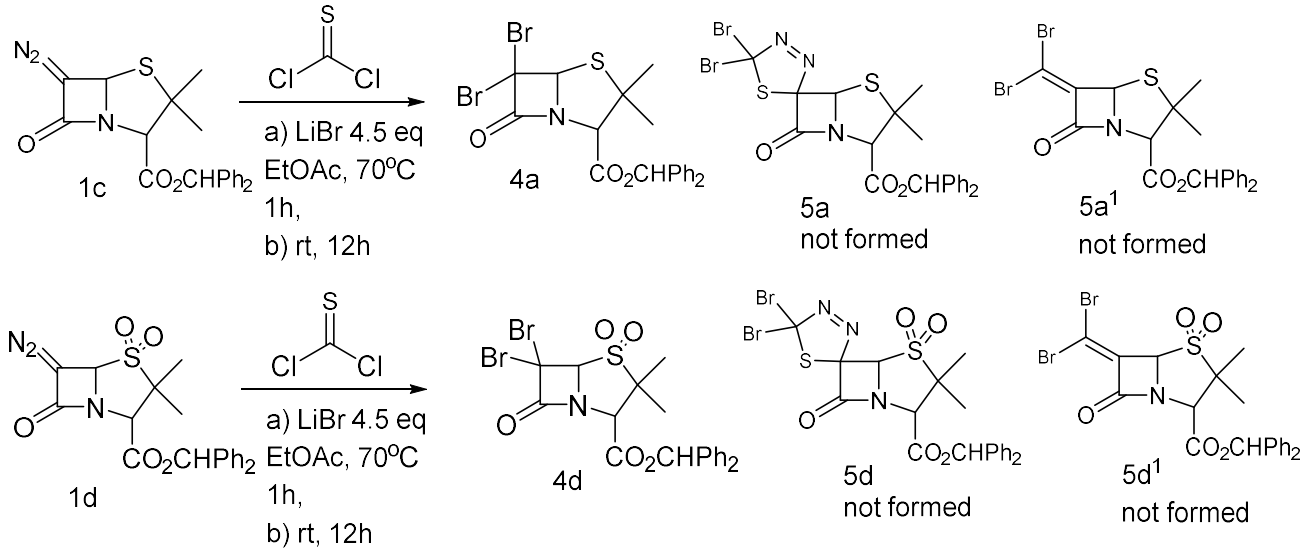
Scheme-4



Bromo version, $CSBr_2$ were prepared by treating thiophosgene[18] with lithium bromide in ethyl acetate at 70°C. FTIR[19] shows slight change in frequency. This $CSBr_2$ is not much explored in organic synthesis[7]. When $CSBr_2$ was treated with diazo **1a**, instead of olefin halo derivatives, it gives dibromo product **4a** exclusively. Mass M/z shows 532, which is consistent with molecular formula 525 and on combination with Lithium ion. The carbon

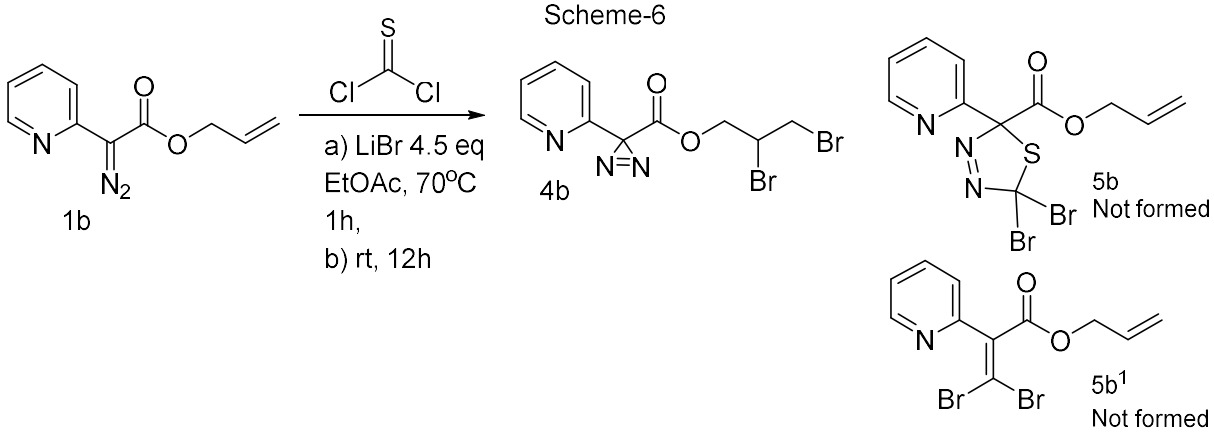
peaks of dibromo bearing carbon in NMR data (58ppm) is matching with predicted value. The Proton NMR data is consistent with reported values[20] where **4a** are prepared by liquid bromine. The sulfone[21] version of diazo **1d** gives its dibromo **4d** exclusively. The spectral data is consistent with reported method[22].

Scheme-5



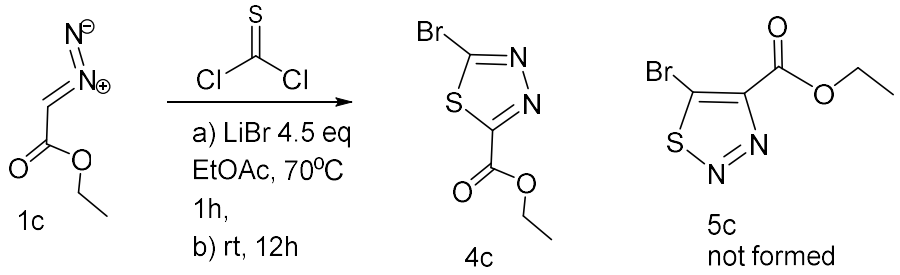
The pyridine diazo **1b**, formed diazine **4b**. Traditionally diazirine conversions occurs at room temperature in THF[23] and by irradiation[24]. The **4b** shows bromine addition occurs on allyl bond, the mass m/z shows 370 [M+(363) + lithium ion (7)], and FT-IR further confirmed the **4b** formation. (scheme-6)

Scheme-6



On treatment with mono substituted diazo **1c**, we isolated the exclusively ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate **4c**. The NMR value are consistent with reported values[25-26] where it synthesized by using Sandmeyer reaction The structure is further confirmed by single crystal data (hard copy only). The ethyl 5-bromo-1,2,3-thiadiazole-2-carboxylate **5c** was not formed under this reaction conditions. (Scheme-7)

Scheme-7

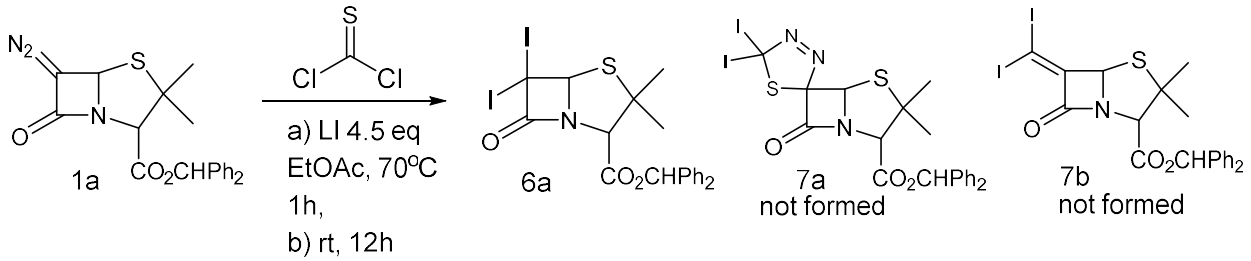


The plausible explanation is, that we used excess (4.5 equivalent) of lithium bromide for preparation of $CSBr_2$. In case of disubstituted diazo, the bromide ion is more reactive then $CSBr_2$, to give the gem-dibromo product, whereas in mono substituted diazo reacted with $CSBr_2$ and gives the expected 5 membered ring. $CSBr_2$ is indeed formed in the reaction, it incorporated in product **4c.**

Substrate.	**$CSBr_2$.**	**Bromide ion**
Disubstituted diazo, 1a,1b,1d,	No	Yes
Mono substituted diazo, 1c	Yes	No

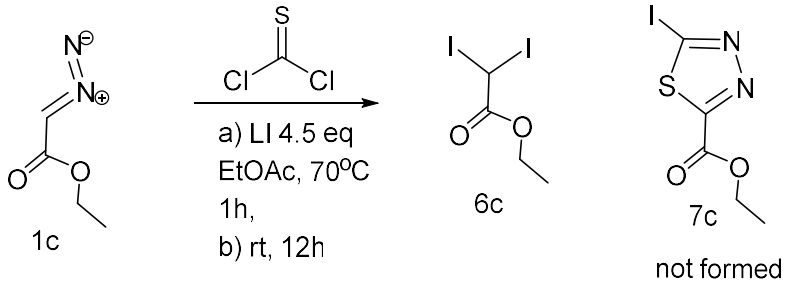
Iodo version, (CSI_2) were prepared by treating thiophosgene[27-28], FTIR shows slight change in frequency. When iodo treated with diazo **1a**, as expected it give diiodo products **6a**. Mass M/z shows 625, which is consistent with molecular formula 618 and on combination with Lithium ion. The carbon peaks of diiodo bearing carbon in NMR data (-7 ppm) is matching with predicted value. This method is addition to literature, where in reported method **6a** obtained one out of multiple products[15]. (Scheme-8)

Scheme-8



On treatment with ethyl diazo acetate **1c**, we isolated the diiodo **6c** product, where diazo displaced by diiodo, there is no cyclic product **7c** were isolated. Independently the **7c** were prepared by using iodine metal were reported[29],[30]

Scheme-9



The plausible explanation is, that we used excess (4.5 equivalent) of lithium iodide for preparation of CSI_2, irrespective of substitution on diazo substrate, the Iodide ion is more reactive then CSI_2, to give the gem-diiodo product.

Substrate.	CSI_2.	Iodide ion
Disubstituted diazo	No	Yes
Mono substituted diazo	No	Yes

Typical Procedure: To a solution of thiophosgene (1.0 eq) in ethyl acetate (25-50 ml) in a single neck round bottom flask, added lithium bromide (4.5 eq) of and heated at 70°C for 1h. Cool to room temperature, then added diazo (0.8 eq) and stir at room temperature for overnight. After reaction complete (checked by TLC), extracted with ethyl acetate (50 mL), washed with water (50 mL), brine solution (50 mL), dried over anhydrous $MgSO_4$

and filter. All volatiles were removed, and the residue was purified using column chromatography (EtOAc:hex) to give products in 55-78% yield.

Products	Dihalo-alkene	Gem-Dihalo	1,3,4-Thiazole	Addition to olefin
Diazo with thiophosgene				
2a	Major		Minor	
2b	Product			
2c			Product	
Diazo with Bromo-thiophosgene and Bromide ion				
4a		Product		
4b				Product
4c			Product	
4d		Product		
Diazo with iodo-thiophosgene and Iodide ion				
6a		Product		
6c		Product		

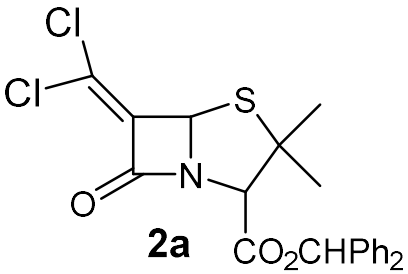
In conclusion, the product formation is depending on substituted diazo substrate, in case of substrate **1a, 1d**, the results are consistent with dihalo substitution, whereas as in case pyridine **1c**, diazine is formed and bromine addition to allyl bond occurs. In case mono substituted diazo substrate **1b**, cyclic 1,2,3-thiadiazoles are formed, except in case iodo version simple substitution occurs.

EXPERIMENTAL PART

All chemicals and other materials were reagent grade unless otherwise specified. All reactions were carried out in a dry nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were obtained on a 300-MHz Bruker Avance NMR spectrometer. All chemicals' shifts are reported in parts per millions. Infrared spectra were obtained on a Nicolet Magna-IR 560 spectrometer E.S.P. Melting points were collected on a TA Instruments DSC 2010

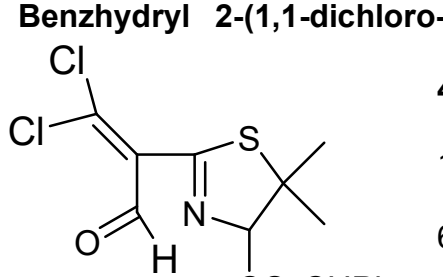
Differential Scanning Calorimeter using a heating rate of 10°C/min and nitrogen as a purge gas.

Benzhydryl 6-(dichloromethylene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2a): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 10H), 6.93 (s, 1H), 5.64 (s, 1H), 4.50 (s, 1H), 1.49 (s, 3H), 1.25 (s, 3H). ^{13}C-NMR (75.0 MHz, $CDCl_3$): δ 168.1, 165.7, 1.38.7, 138.6, 138.5, 128.6, 128.5, 128.4, 128.2, 127.5, 127.2, 126.8, 78.6, 69.9, 64.8, 33.2, 25.7.



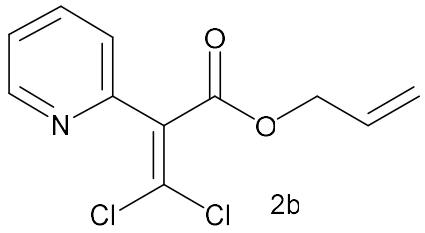
2a

Benzhydryl 2-(1,1-dichloro-3-oxoprop-1-en-2-yl)-5,5-dimethyl-4,5-dihydrothiazole-4-carboxylate (3a): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.16 (s, 10H), 6.80 (s, 1H), 5.05 (s, 1H), 144-1.35 (d, 6H). ^{13}C-NMR (75.0 MHz, $CDCl_3$): δ 186.8, 165.0, 138.7, 128.6, 128.5, 128.4, 128.2, 127.5, 127.0, 79.5, 65.6, 53.6, 24.6. Mass m/z: 000.00. IR (KBr) (wavenumber, cm^{-1}): 3062 (C-Cs), 2061 (S-C=N), 1744 (H-C=O), 1670 (O-C=O), 1495, 1453 (C=Cs), 1193 (C-Cl), 952 (C-Cb). Mass m/z: (M+), 447.2 observed.



3a

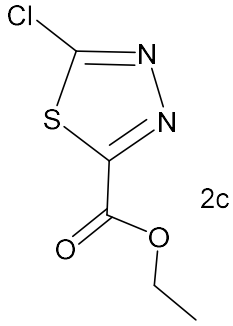
allyl 3,3-dichloro-2-(pyridin-2-yl) acrylate (2b): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.25-8.23 (d, 1H, *J* = 5.6 Hz), 7.62 (s, 1H), 7.30 (s, 1H), 7.13-6.11 (t, 1H, *J* = 2.45 Hz), 5.51-5.47 (d, 1H, *J* = 12.86 Hz), 5.35-5.33 (s, 1H, *J* = 7.41 Hz), 4.98 (s, 2H). ^{13}C-NMR (75.0 MHz, $CDCl_3$): δ 160.3, 134.4, 131.4, 129.1, 128.4, 125.5, 118.4, 118.3, 116.2, 64.9. IR (KBr) (wavenumber, cm^{-1}): 3100 (C-



2b

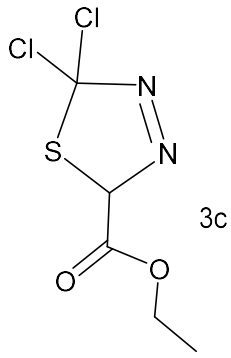
Cs), 1719 (O-C=O), 1515, 1437 (C=Cs), 1193 (C-Cl), 934 (C-Cb). Mass m/z (M-57+Li) 210 observed.

Ethyl 5-chloro-1,3,4-thiadiazole-2-carboxylate[16] (2c): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.55-4.50 (q, 2H, *J* = 5.35 Hz), 1.49-1.25 (t, 3H, *J* = 5.37 Hz). ^{13}C-NMR (75.0 MHz, $CDCl_3$): δ 162.1, 158.6, 157.6, 63.7, 14.0.



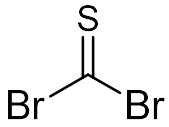
2c

Ethyl 5,5-dichloro-2,5-dihydro-1,3,4-thiadiazole-2-carboxylate (3c): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.29 (s, 1H), 4.28-4.17 (m, 2H), 1.31-1.23 (m, 3H). ^{13}C-NMR (75.0 MHz, $CDCl_3$): δ 165.8, 103.4, 63.6, 48.9, 13.9.



3c

Carbonothioic dibromide (): To a solution of 2.0 g (17.3 mmol) of thiophosgene in ethyl acetate (50 ml) in a single neck round bottom flask, added 6.8g of (4.4 eq) of lithium bromide (Mol.Wt 87.112 g/mol) and heated at 70^{o}C for 1h. Cool to room temperature and used in next reactions. IR (KBr) (wavenumber, cm^{-1}): 1635 (C=S), 1262 (Br-C), 1503, 1098 (C-Cb).



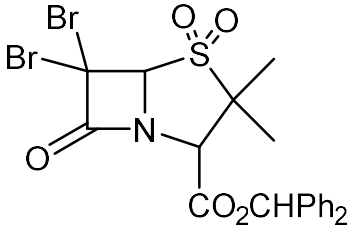
benzhydryl 6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate[22] (4a): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.28 (m, 10H), 6.93 (s. 1H, benzylic), 5.82 (s, 1H, C5 CH), 4.62 (s, 1H, C3 CH), 1.59 (s, 3H, Me), 1.25 (s, 3H, Me). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 165.5, 164.3, 138.8, 138.7. 128.54, 128.52, 128.4, 128.2, 127.3, 126.9, 80.8, 78.6, 69.6, 64.8, 58.6, 33.6, 25.5. IR (KBr) (wavenumber, cm^{-1}): 3062 (C-Cs), 1783 (O-C=O), 1745 (HN-C=O), 1494, 1452 (C=Cs), 1255 (C-Br), 992 (C-Cb). Mass m/z (M+Li), 532.1 observed.

2,3-dibromopropyl 3-(pyridin-2-yl)-3H-diazirine-3-carboxylate (4b): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.81-8.79 (d, 1H, *J* = 5.2 Hz), 8.20-8.18 (d, 1H, *J* = 3.68 Hz), 7.56-7.52 (dd, 1H, *J* = 5.2 & 0.5 Hz), 7.18-7.16 (t, 1H, *J* = 6.0 Hz), 4.82 (m, 2H), 4.50-4.47(m, 1H), 3.85-3.80 (m, 2H). ^{13}C-NMR (75.0 MHz, $CDCl_3$): δ 160.0, 134.9, 129.7, 128.2, 125.9, 118.9, 116.5, 65.9, 45.9, 32.3. IR (KBr) (wavenumber, cm^{-1}): 3103 (C-Cs), 1722 (O-C=O), 1514, 1434 (C=Cs), 1198 (C-Br), 981 (C-Cb). Mass m/z: (M+Li) 370.1 observed.

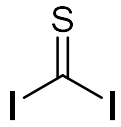
Ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate[26] (4c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56-4.51 (q, 2H, *J* = 5.32 Hz), 1.48-1.45 (d, *J* = 5.33 Hz, 3H). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 163.5, 157.3, 144.6, 63.6, 13.9. IR (KBr) (wavenumber, cm^{-1}): 2986 (C-Cs), 1749 (O-C=O), 1473, 1452 (C=Cs), 1266 (C-Br), 1030 (C-Cb). Mass m/z: (M+Li) 242.9 observed

4c

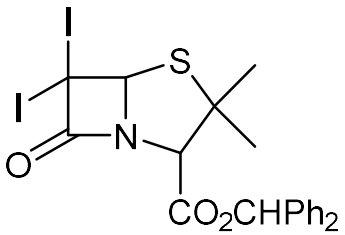
benzhydryl 6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide[22] (4d): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.35-7.34 (m, 10H), 6.96 (s. 1H), 4.99 (s, 1H), 4.60 (s, 1H), 1.58 (s, 3H), 1.12 (s, 3H).



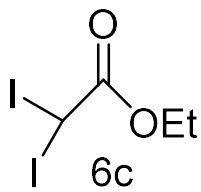
Carbonothioic diiodide (): To a solution of 1.0 g (8.65 mmol) of thiophosgene in ethyl acetate (25 ml) in a single neck round bottom flask, added 5.2 g of (4.4 eq) of lithium Iodide (Mol.Wt 133.84 g/mol) and heated at 70^{o}C for 1h. Cool to room temperature and used in next reactions. IR (KBr) (wavenumber, cm^{-1}): 1594 (C=S), 1270 (I-C), 1503, 1044 (C-Cb).



benzhydryl 6,6-diiodo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (6a): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 6.92, (s, 1H), 5.80 (s, 1H), 4.62 (s, 1H), 1.60 (s, 3H), 1.25 (s, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 167.3, 165.7, 138.9, 138.8, 81.7, 78.6, 70.2, 65.8, 34.0, 26.3, -7.46 (C-I). IR (KBr) (wavenumber, cm^{-1}): 3055 (C-Cs), 1787 (O-C=O), 1745 (HN-C=O), 1495, 1453 (C=Cs), 1265 (C-I), 738 (C-Cb). Mass m/z: (M+Li) 625.9 observed.



Ethyl 2,2-diiodoacetate[30] (6c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (s, 1H), 4.31-4.24 (q, 2H, *J* = 7.1 Hz), 1.33-1.30 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 166.0, 63.4, 13.6. IR (KBr) (wavenumber, cm^{-1}): 2981 (C-Cs), 1724 (O-C=O), 1254 (C-I), 1023 (C-Cb). Mass m/z: (M+) 285.1 observed.



ACKNOWLEDGMENTS

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