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Photochemical reaction of pyrimidine-2-thione derivatives

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ABSTRACT

The photocycloaddition of pyrimidine-2-thione derivatives **(1)** and **(7)** to alkynes **(2a,b)** and alkene **(9)** are studied. Irradiation of dioxane solution of **(1)** in the presence of alkynes **(2a,b)** produced the thiol derivatives **(3a,b)** through ring cleavage of thietene **(5)**. Irradiation of **(1)** in the presence of alkenes **(9)** under the same conditions produced the corresponding photoproducts **(12)** and **(13)** respectively. The structure of all products was confirmed by analytical spectral data.

KEYWORDS

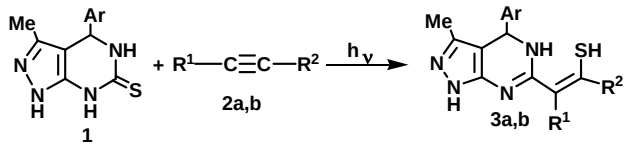
Thiocarbonyl;
Alkynes;
Alkenes;
Photocycloaddition;
High pressure mercury lamp.

INTRODUCTION

The photochemistry of thiocarbonyl compounds has extensively high attention[1-4]. The observed photoreactions of thiocarbonyl compounds often follow a different course from their carbonyl compounds analogues. The majority of these reported involving thioketenes that undergo [2+2] cycloaddition to alkenes, alkynes, imines, inter- and intramolecular H-abstraction, and photo-oxidation[5,6]. Some reports deal with the photochemical reactions involving the C=S group of thioamides[7]. In particular, they gave, by [2+2] photocycloadditon with alkenes or alkynes, thietanes as a primary adducts[8] that are often unstable and are transformed into their fragmentation products. This may be ascribed to the participation of the lone-pair electrons of the N-atom which facilitate the C-S bond cleavage of the thietane ring[9]. In this report the photocycloaddition reactions of pyrimidine-2-thione derivatives[10,11] **(1)** with different alkynes and alkenes were studied to furnish the corresponding thiol derivatives.

RESULTS AND DISCUSSION

Irradiation of a dioxane solution of 4-(2,5-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*d*]pyrimidine-6-thione **(1)** with a high pressure mercury lamp through a Pyrex filter under Nitrogen in the presence of alkynes **(2a-c)** furnished the corresponding thiol derivatives **(3a-b)**.

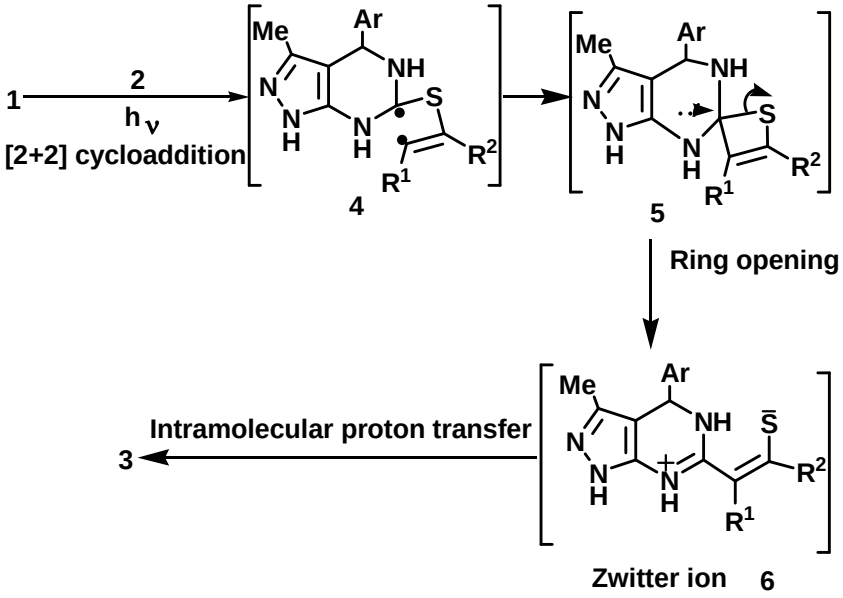


Ar = 2,5-dimethoxyC_6H_3

	R^1	R^2
2, 3a,	COOMe	COOMe
b,	COOH	COOH

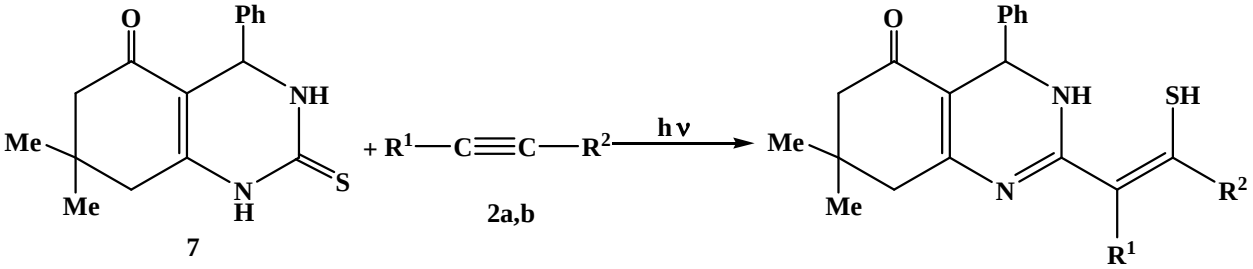
The formation of 2-(2-mercapto-alkyl)pyrimidine **(3)** can be best explained by the intermediacy of the spirocyclic thietene **(5)**. The latter is formed regioselectively by photochemical [2+2] cycloaddition of C=C of pyrimidine-2-thione **(1)** and the C≡C of alkyne **(2)** *via* the more stable biradical intermediate[12-14] **(4)**. Compound **(5)** undergoes ring cleavage

in the presence of the lone-pair electrons of the N-atom to afford the Zwitter ion **(6)**. Finally, the intramolecular proton transfer occurs to form the final isolated product **(3)** (Scheme 1).



Scheme 1

In a similar manner 7,7-dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1*H*)-one was treated with **(2a,b)** under the experimental conditions, where by compound **(8a,b)** was formed.



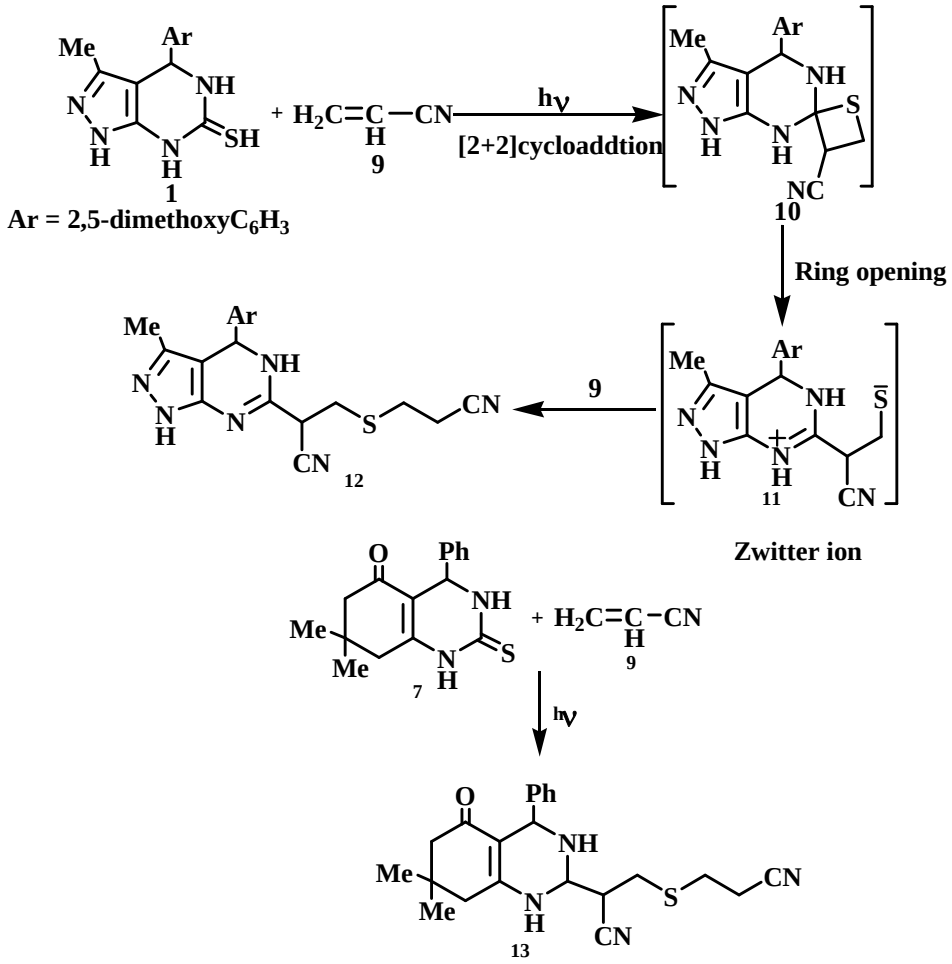
	R^1	R^2
2, 8a,	COOMe	COOMe
b,	COOH	COOH

The structure of the new photoproducts was elucidated on the basis of their spectral and analytical data. As an example the 1H-NMR spectrum of **(3a)** revealed the characteristic signal of the SH group at $\delta = 1.03$ ppm; the IR spectrum exhibited the characteristic thiol absorption band at 2550 cm^{-1}. The UV spectrum of **(3a)** revealed $\lambda_{max} = 463$ nm, that establish the conjugated structure. Such as compound **(8a)** showed ^{1}H-NMR at δ 0.89 (S, 1H, SH); 1.50 (s, 3H, CH_3); 1.93 (s, 3H, CH_3); 2.01 (s, 2H, -CH_2); 2.29 (s, 2H, -CH_2); 3.76 (s, 3H, -$COOCH_3$); 3.82 (s, 3H, -$COOCH_3$); 4.81 (s, 1H, -CH); 7.01-7.65 (m, 5H, 5 aromatic protons); 8.90 (s, 1H, NH); and Mass spectrum of compound **(8a)** showed molecular ion peak at m/z: 430 [M^+, 4.20%]; which proves the molecular ion ($C_{22}H_{24}N_2O_5S$).

Mass spectrum of compound **(3b)** showed molecular ion peak at m/z: 420 [M^+, 2.88%]; which proves the molecular ion ($C_{18}H_{18}N_4O_6S$).

The photocycloaddition reactions of **(1)** and **(7)** with electron-deficient alkenes like acrylonitrile is studied. Irradiation of a dioxane solution of **(1)** and **(7)** in the presence of excess of acrylonitrile **(9)** under the same previously explained conditions led to the formation of the

product **(12)**. In spite of, the presence of two regioisomeric modes of cycloaddition of a thione with acrylonitrile. Compound **(12)** in the present work is the only isolable isomer that could be obtained and identified. Similar sulphide adduct was previously detected and identified as a product from the photoreaction of benzothaizole-2-thione with dimethylethylene (DME)[15]. The presence of additional products in the photochemical reaction of **(1)** with acrylonitrile **(9)** could also be detected (column chromatography). However, these minor unspecified products could be isolated. Further studies are now under investigation to isolate and identify these products. Formation of compound **(12)** could be explained by assuming that the Zwitter ion **(11)** formed at first *via* the thietane intermediate[1] **(10)**; then reacted with another molecule of **(9)** to furnish the corresponding photoadduct **(12)** similarly photocycloaddition reaction of **(7)** with acrylonitrile **(9)** under the same condition to



Scheme 2

gives **(13)** (Scheme 2).

The mass spectrum of compound **(12)** revealed the molecular ion peaks [M^+] at m/z = 410 for the correct molecular weight of **(12)**. The IR and ^{1}H-NMR spectra revealed the disappearance of the characteristic signal of the SH group. All the spectroscopic and microanalytical data were in accordance with the suggested structure. Such as compound **(13)** showed ^{1}H-NMR at δ 0.97 (s, 3H, CH_3); 1.93 (s, 3H, CH_3); 2.01 (s, 2H, -CH_2); 2.29 (s, 2H, -CH_2); 2.41 (t, 2H. CH_2, *J* =6.0 Hz); 2.62 (d, 2H, CH_2, J =8 Hz), 3.64 (t, 2H, CH_2, *J* =6.0 Hz), 4.75 (s, 1H, CH); 4.97 (t, 1H, CH, J =8.0 Hz), 7.32–7.45 (m, 5H, 5 aromatic protons and NH proton), 8.55 (s, 1H, NH); 9.56 (s, 1H, NH); and Mass spectrum of compound **(13)** showed molecular ion peak at m/z: 396 [M^+, 2.88%].

EXPERIMENTAL

Melting points were determined on an electrother-

mal apparatus (Buchi 535, Switzerland) in an open capillary tube and are uncorrected. IR spectra expressed in (cm^{-1}) were recorded in KBr pellets on a PA-9721 IR spectrophotometer. ^{1}H-NMR & ^{13}C-NMR spectra were obtained on a Varian EM-390 (270 and 500 MHz) spectrometer in CD_3Cl as solvent, using TMS as internal reference and chemical shifts (δ) are expressed in ppm. Mass spectra were recorded on Kratos (75 e-v) Ms Equipment. Elemental analyses were carried out by the micro-analytical unit at the National Research Centre, Giza, Egypt.

All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (245 and 365 nm) for detection. Column chromatography was carried out on a Baker silica gel powder (60-200 mesh).

The photoreaction of 4-(2,5-dimethoxyphenyl)-3-methyl-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*d*]pyrimidine-6-thione (1) and 7,7-dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydroquinazolin-5(1H)-one (7) with alkynes (2a,b) or acrylonitrile

(a) General procedure

A solution of **(1)** or **(7)** (0.03 g, 0.01 mol) in dioxin (300 ml) in the presence of excess of alkynes **(2a,b)** or acrylonitrile **(9)** in a Pyrex vessel under N_2 was irradiated with a high pressure Mercury lamp (HP, Philips, 125 W), until completion of the reaction at room temperature. The reactions were monitored by thin layer chromatography (TLC) using aluminum sheets with silica gel 60 F254 (Merck). After removal of the solvent, the residue was chromatographed (silica gel, 60 mesh) with suitable solvent to yield the photoproducts **(3a,b)** or **(8a,b)** and **(12)** or **(13)**.

(b) Dimethyl 2-[4-(2,5-dimethoxy-phenyl)-3-methyl-4,5-dihydro-1*H*-pyr-azolo[3,4-d]pyrimidin-6yl]-3-mercapto-but-2-enedioat 3(a)

Irradiation time 25 hours,eluent (ethyl acetate : petroleum ether 40-60 ºC, 8 : 2); oil; yield (92%); Ms (m/z, %): 446 [M^+, 8.20%]; IR (film, cm^{-1}): 3429 (NH); 3126 (C-H, aromatic); 2926, 2906, 2862 (CH_3); 2550 (SH); 1731 (C=O); 1650 (C=O). UV λ_{max} = 463 nm. ^{1}H-NMR (270 MHz, $CDCl_3$-d_1, TMS): δ 1.03 (S, 1H, SH); 1.78 (S, 3H, -CH_3); 3.64 (s, 3H, -OCH_3); 3.72 (s, 3H, -OCH_3); 3.76 (s, 3H, -$COOCH_3$); 3.77 (s, 3H, -$COOCH_3$); 4.86 (s, 1H, -CH); 6.25-7.01 (m, 4H, 3 aromatic protons and NH proton); 12.10 (s, 1H, NH). Anal. Calcd. For $C_{20}H_{22}N_4O_6S$: C, 53.80%; H, 4.97%; N, 12.55%; Found: C, 53.65%; H, 4.81%; N, 12.30%.

(c) (2E)-2-[4-(2,5-dimethoxyphenyl)-3-methyl-4,5-dihydro-1*H*-pyr-azolo[3,4-d]pyrimidin-6-yl]-3-sulfanylbut-2-enedioic acid (3b)

Irradiation time 23 hours, eluent (ethyl acetate : petroleum ether 40-60 ºC, 6 : 2); oil; yield (86%); Ms (m/z, %): 420 [M^+, 2.88%]. IR (film, cm^{-1}): 3440 (NH); 3125 (C-H, aromatic); 2921, 2900, 2860 (CH_3); 2551 (SH); 1733 (C=O); 1658 (C=O). UV λ_{max} = 452 nm. ^{1}H-NMR (270 MHz, $CDCl_3$-d_1, TMS): δ 1.01 (S, 1H, SH); 1.76 (S, 3H, -CH_3); 3.64 (s, 3H, -OCH_3); 3.72 (s, 3H, -OCH_3); 4.80 (s, 1H, -CH); 6.20-6.85 (m, 4H, 3 aromatic protons and NH proton); 11.01 (s, 1H, COOH, exchangeable with D_2O); 11.10 (s, 1H, COOH, exchangeable with D_2O); 12.10 (s, 1H, NH). Anal. Calcd. For $C_{18}H_{18}N_4O_6S$: C, 51.67%; H, 4.34%; N, 13.39%. Found: C, 51.33%; H, 4.14%; N, 13.05%.

(d) Dimethyl 2-(7,7-dimethyl-5-oxo-4-phenyl-3,4,5,6,8-hexahydro-quina-zolin-2-yl)-3-mercapto-but-2-enedioate (8a)

Irradiation time 20 hours, eluent (ethyl acetate : petroleum ether 40-60 ºC, 7 : 2); oil; yield (95%); Ms (m/z, %): 430 [M^+, 4.20%]. IR (film, cm^{-1}): 3393 (NH); 3125 (C-H, aromatic); 2954, 2920, 2810 (CH_3); 2465 (SH); 1736 (C=O); 1694 (C=O); 1664 (C=O). UV λ_{max} = 481 nm. ^{1}H-NMR (270 MHz, $CDCl_3$-d_1, TMS): δ 0.89 (S, 1H, SH); 1.50 (s, 3H, CH_3); 1.93 (s, 3H, CH_3); 2.01 (s, 2H, -CH_2); 2.29 (s, 2H, -CH_2); 3.76 (s, 3H, -$COOCH_3$); 3.82 (s, 3H, -$COOCH_3$); 4.81 (s, 1H, -CH); 7.01-7.65 (m, 5H, 5 aromatic protons); 8.90 (s, 1H, NH). Anal. Calcd. For $C_{22}H_{24}N_2O_5S$: C, 61.67%; H, 5.65%; N, 6.54%. Found: C, 61.52%; H, 5.30%; N, 6.24%.

(e) (2E)-2-(7,7-dimethyl-5-oxo-4-phenyl-3,4,5,6,7,8-hexahydroquinazolin-2-yl)-3-sulfanylbut-2-enedioic acid (8b)

Irradiation time 20 hours, eluent (ethyl acetate : petroleum ether 40-60 ºC, 9 : 2); oil; yield (75%); Ms (m/z, %): 402 [M^++2, 6.24%]; 397 [M^+-3, 4.87%]. IR (film, cm^{-1}): 3425 (NH); 3125 (C-H, aromatic); 2925,

2920, 2810 (-CH_3); 2445 (SH); 1730 (C=O); 1672 (C=O); 1664 (C=O). UV λ_{max} = 464 nm. ^{1}H-NMR (270 MHz, $CDCl_3$-d_1, TMS): δ 0.89 (S, 1H, SH); 1.01 (s, 3H, CH_3); 1.93 (s, 3H, CH_3); 2.01 (s, 2H, -CH_2); 2.29 (s, 2H, -CH_2); 4.81 (s, 1H, -CH); 7.01-7.65 (m, 5H, 5 aromatic protons); 8.90 (s, 1H, NH); 10.01 (s, 1H, COOH, exchangeable with D_2O); 13.10 (s, 1H, COOH, exchangeable with D_2O). Anal. Calcd. For $C_{20}H_{20}N_2O_5S$: C, 59.99%; H, 5.03%; N, 7.00%. Found: C, 59.66%; H, 4.93%; N, 6.91%.

(f) 3-[(2-cyanoethyl)sulfanyl]-2-[4-(2,4-dimethoxyphenyl)-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-6-yl] propionitrile (12)

Irradiation time 4 h, eluent (MeOH), oil; Yield (74%); MS (m/z) = 410 [M^+, 6.24%]. IR (film, cm^{-1}): 3396 (NH), 2935 (CH3), 2191 (CN). 1H-NMR (270 MHz, CDCl3-d1, TMS): δ 1.07 (s, 3H, CH_3); 2.36 (t, 2H. CH_2, J =6.0 Hz), 2.62 (d, 2H, CH2, J =8 Hz), 3.64 (t, 2H, CH_2,J =6.0 Hz), 3.76 (s, 3H, -OCH_3); 3.81 (s, 3H, -OCH_3); 4.85 (s, 1H, CH); 4.97 (t, 1H, CH, J =8.0 Hz), 7.30–7.59 (m, 4H, 3 aromatic protons and NH proton), 8.55 (s, 1H, NH); 11.91 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{22}N_6O_2S$: C, 58.52%; H, 5.40%; N, 20.47%. Found: C, 58.32%; H, 5.21%; N, 20.25%.

(g) 3-(2-Cyano-ethylsulfanyl)-2-(7,7-dimethyl-5-oxo-4-phenyl-1,2,3,4,5,6,7,8-octahydro-quinazolin-2-yl)propionitrile (13)

Irradiation time 7 h, eluent (EtOH), oil; Yield (64%); MS (m/z) = 396 [M^+, 2.88%]. IR (film, cm^{-1}): 3425 (NH), 2925 (CH3), 2211 (CN). 1H-NMR (270 MHz, CDCl3-d1, TMS): δ 0.97 (s, 3H, CH_3); 1.93 (s, 3H, CH_3); 2.01 (s, 2H, -CH_2); 2.29 (s, 2H, -CH_2); 2.41 (t, 2H. CH_2, J =6.0 Hz); 2.62 (d, 2H, CH_2, J =8 Hz), 3.64 (t, 2H, CH_2, J =6.0 Hz), 4.75 (s, 1H, CH); 4.97 (t, 1H, CH, J =8.0 Hz), 7.32–7.45 (m, 5H, 5 aromatic protons and NH proton), 8.55 (s, 1H, NH); 9.56 (s, 1H, NH). Anal. Calcd. For $C_{22}H_{25}N_4OS$: C, 66.97%; H, 6.64%; N, 14.20%. Found: C, 66.83%; H, 6.51%; N, 14.02%.

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