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A Convenient Synthesis of 2-Azido and 2-Thiocyanato-2,3-Unsaturated Cyclic Ketones

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2-Azido and 2-thiocyanato-2,3-unsaturated ketones were synthesized by utilizing functionalization of 5- or 6-membered cycloalkane-1,2-diones, namely diosphenols, with dimethylthiocarbomoyl chloride, which activates the system towards reaction with nucleophiles in acidic conditions. Replacement of the enolic oxygen of the diosphenols with azide and thiocyanate may be achieved by treating their dimethylthiocarbamates with sodium azide or potassium thiocyanate in boiling acetonitrile/acetic acid.

Key Words: Azides, thiocyanates, enols, deoxygenation, 1,2-cyclic diketones.

Introduction

2-Azido and 2-thiocyanato-2,3-unsaturated ketones are quite attractive intermediates in organic synthesis. One reported procedure for obtaining similar azides was the result of an unexpected elimination of the diphenylphosphoryl group after the ring opening of 2,3-epoxy ketones with diphenyl phosphorazidate [DPPA, $(PhO)_2P(O)N_3$].[1] Another procedure describes the formation of 2-azido-2-cyclohexenone, possibly after the conversion of 2-cyclohexenone to 1,2-diazide in the presence of $Mn(OAc)_3$ in acetonitrile-TFA.[2] Hypervalent iodine compounds are also utilized for the synthesis of vicinal diazides in AcOH from alkenes.[3] 1,2-Bis azidonation of trialkylsilyl ethers via an azido-radical addition process promoted by TEMPO is another method worthy of mention.[4] 2-Thiocyanato-2-ethylenic carbonyl compounds from 2,3-epoxy ketones have also been reported and some reactions of these compounds were examined.[5] Preparation of 2-thiocyanato-2-ethylenic carbonyl compounds using potassium and ammonium thiocyanates gave poor results with this method. Instead, thiocyanato derivatives were prepared with $PPh_3(SCN)_2$.

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Dimethylthiocarbamoylation,[6] followed by treatment with lithium halides in acetic acid is an efficient method to convert the enolic oxygen of diosphenols to chlorides, bromides, and hydrogen. Some 2-chloro- and 2-bromo-2,3-unsaturated ketones[7,8] were synthesized using this method. Reduction of enolic oxygen was afforded when LiI was used.[9]

Herein we report a new procedure for synthesizing 2-azido- and 2-thiocyanato-2,3-unsaturated ketones in fair yields by treating the diosphenol dimethylthiocarbamates with sodium azide or potassium thiocyanate in a boiling acetic acid-acetonitrile mixture.

Experimental

General Methods

All the required fine chemicals were used directly without purification. Reactions were performed in an acetonitrile-acetic acid (1:1) mixture. Column chromatography was performed on silica gel (0.063-0.200 mm) with EtOAc-hexane (1:8). TLC was performed on silica gel 60F-254 precoated sheets. IR spectra were taken with Shimadzu IR 470 or ATI Unicam Mattson 1000 Fourier Transform IR spectrophotometers. ^{1}H NMR spectra were recorded in deuteriochloroform solution with a Varian Mercury Plus 300 MHz spectrometer. ^{13}C spectra were recorded at 75 MHz. Mass spectra were measured on a Thermo Trace GC Ultra DSQ II instrument, with electron impact at 70 eV. Reaction mixtures were injected into the GC-MS after dilution and were worked up with methylene chloride. C and H analysis could not be performed due to the high air sensitivity of the products. Only isolated yields were reported. Diosphenol thiocarbamates (1b-5b) were prepared from two-phase reaction of the related diosphenol with N,N-dimethyl thiocarbamoyl chloride in a $CHCl_3$-H_2O mixture, according to a previously reported method.[7]

General Procedure for Preparation of 2-Azido and 2-Thiocyanato-2,3-Unsaturated Ketones from Diosphenol Thiocarbamates

2-Azidocyclopent-2-enone (1c)

To a magnetically stirred boiling solution of 2-[(dimethylthiocarbamoyl)-oxy]-2-cyclopenten-1-one (**1b**, 0.185 g, 1 mmol) in 10 mL of an acetic acid/acetonitrile mixture (1:1) was added sodium azide (0.65 g 10 mmol). The reaction mixture was cooled after 2 h of refluxing and poured into 20 mL of water. Acetic acid was neutralized with sodium bicarbonate and then the mixture was extracted with two 20-mL portions of methylene chloride. The organic extracts were washed with 30 mL of brine, dried over anhydrous calcium chloride, and then evaporated, giving 0.14 g of crude product, which was then chromatographed on silica gel packed in ethyl acetate-hexane (1:8), yielding 0.05 g (41%) of colorless oil. NMR indicated that it was fairly pure.

IR: 3088, 2928, 2128, 1708, 1616, and 1440 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47-2.60 (m, 4H) and 6.86 (t, J = 3.08 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4, 34.2, 140.0, 142.8, and 203.1.

MS (EI): m/z (%) = no molecular ion, 95 (1), and 67 (100).

Other 2-azido and 2-thiocyanato-2,3-unsaturated ketones were synthesized according to general procedures. Ten

equivalent potassium thiocyanates were used for the synthesis of 2-thiocyanato-2,3-unsaturated ketones.

2-Thiocyanatocyclopent-2-enone (1d)

Yield: 43%; colorless oil.
IR: 3088, 2944, 2176, 1712, 1590, and 1430 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60-2.87 (m, 4H) and 7.78 (t, J = 3.08 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6, 34.5, 108.6, 132.5, 160.3, and 202.0.
MS (EI): m/z (%) = 138.8 (M^+, 100), 110.9 (10), 84.9 (42), and 53 (30).

2-Azidocyclohex-2-enone (2c)

Yield: 66%, colorless oil.
IR: 3058, 2928, 2128, 1683, 1619, and 1456 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.0 (quintet, 2H), 2.44 (quartet, 2H), 2.52 (t, J = 6.59 Hz, 2H), and 6.43 (t, J = 4.69 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 25.4, 38.5, 133.0, 135.5, and 194.2.
MS (EI): m/z (%) = no molecular ion, 108.9 (6), 81 (12), and 67 (68).

2-Thiocyanatocyclohex-2-enone (2d)

Yield: 16%; yellowish oil.
IR: 3056, 2960, 2176, 1664, 1600, and 1452 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.1 (quintet, 2H), 2.53-2.68 (m, 4H), and 7.31 (t, J = 4.40 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 27.5, 38.0, 110.5, 128.1, 147.2, and 193.7.
MS (EI): m/z (%) = 152.9 (M^+, 100), 124.9 (24), 96.9 (50), and 67 (34).

5-Allyl-2-azido-5-methylcyclopent-2-enone (3c)

Yield: 45%; colorless oil.
IR: 3088, 2928, 2128, 1708, 1620, 1452, and 1347 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 3H), 2.23-2.61 (dd, J = 3.30, 19.43 Hz, 2H), 2.13-2.34 (m, 2H), 5.04-5.11 (m, 2H), 5.55-5.70 (m, 1H), and 6.75 (t, J = 3.30 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.8, 37.7, 42.5, 46.6, 119.0, 133.2, 138.3, 140.2, and 207.4.
MS (EI): m/z (%) = no molecular ion, 136 (68), and 108 (28).

5-Allyl-5-methyl-2-thiocyanatocyclopent-2-enone (3d)

Yield: 67%; colorless oil.
IR: 3104, 2992, 2928, 2176, 1712, 1638, 1590, 1452, 1430, and 1372 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 2.15-2.36 (m, 2H), 2.48-2.86 (dd, J = 3.08, 19.79 Hz, 2H), 5.05-5.11 (m, 2H), 5.53-5.59 (m, 1H), and 7.68 (t, J= 3.08 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 41.6, 42.5, 48.0, 108.7, 119.6, 130.0, 132.6, 158.1, and 206.5.
MS (EI): m/z (%) = 192.9 (M^+, 100), 151.9 (72), and 123.9 (46).

6-Allyl -2-azido-6-methyl cyclohex-2-enone (4c)

Yield: 42%; colorless oil.
IR: 3072, 2928, 2128, 1724, 1619, 1449, and 1376 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.71-1,97 (m, 2H), 2,18-2,46 (m, 4H), 5.04-5.12 (m, 2H), 5.68-5.77 (m, 1H), and 6.34 (t, J = 4.40 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.88, 21.96, 33.0, 41.1, 45.5, 118.9, 131.3, 133.5, 134.0, and 198.6.
MS (EI): m/z (%) = no molecular ion, 150.0 (6), 123.0 (100), 109.0 (84), and 95 (28).

6-Allyl-6-methyl-2-thiocyanatocyclohex-2-enone (4d)

Yield: 53%; colorless oil.
IR: 3072, 2928, 2160, 1731, 1670, 1606, 1446, 1420, and 1376 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 3H), 1.80-2.07 (m, 2H), 2.18-2.41 (m, 2H), 2.56-2.63 (m, 2H), 5.04-5.14 (m, 2H), 5.64-5.74 (m, 1H), and 7.26 (t, J = 4.40 Hz , 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 24.7, 33.0, 41.2, 46.2, 110.7, 119.6, 127.4, 133.2, 145.5, and 198.4.
MS (EI): m/z (%) = 206.9 (M^+, 100), 165.9 (26), 149.0 (32) 124.9 (50), 96.8 (90).

2-Azido-5,5-dimethylcyclopent-2-enone (5c)

Yield: 50%; colorless oil.
IR: 3056, 2928, 2123, 1724, 1616, 1456, and 1379 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 6H), 2.37 (d, J = 3.22 Hz, 2H), and 6.70 (t, J = 3.22 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 41.1, 43.3, 137.4, 139.9, and 208.1.
MS (EI): m/z (%) = no molecular ion, 122.9 (10), and 94.9 (100).

5,5-Dimethyl-2-thiocyanatocyclopent-2-enone (5d)

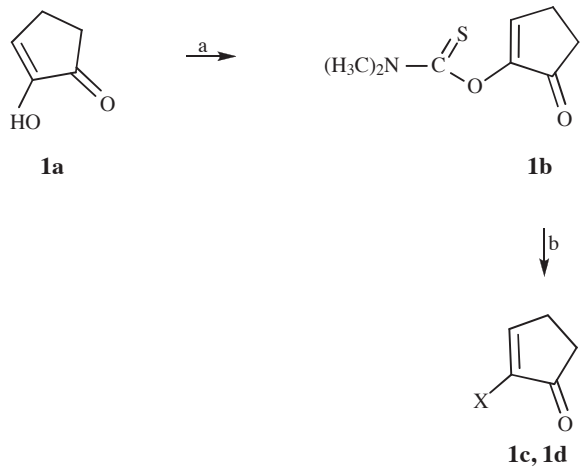
Yield: 68%; yellowish oil.
IR: 3066, 2970, 2164, 1724, 1589, 1474, and 1397 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (s, 6H), 2.68 (d, J = 2.93 Hz, 2H), and 7.68 (t, J = 2.93 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 44.6, 45.0, 110.0, 129.4, 157.4, and 206.9.
MS (CI): m/z (%) = 168.0 (M^++1, 100), 109.1 (7), and 77 (8).

Results and Discussion

Five different diosphenol thiocarbamates, namely 2-[(dimethylthiocarbamoyl)oxy]-2-cyclopenten-1-one (**1b**), 2-[(dimethylthiocarbamoyl)oxy]-2-cyclohexen-1-one**(2b),** 5-allyl-5-methyl-2-[(dimethylthiocarbamoyl) oxy]-2-

cyclopenten-1-one (**3b**), 6-allyl-6-methyl-2-[(dimethylthiocarbamoyl)oxy]-2-cyclohexen-1-one (**4b**), and 5,5-dimethyl-2-[(dimethylthiocarbamoyl)oxy]-2-cyclopenten-1-one (**5b**), were synthesized from related diosphenols in a chloroform-water two-phase system. Then, the thiocarbamate derivatives were converted to azides or thiocyanates, as illustrated in Figure 1.

Related diosphenols were synthesized from commercially available starting materials via SeO_2 oxidation of ketones.[10] O-allylation was followed by Claisen rearrangement of the 3-methyl-1,2-cyclic diones or methylation of the protected 3-methyl-1,2-cyclopentandione.



Reagents; (a) $Me_2NC(S)Cl$, $LiOH.H_2O$, and $CHCl_3/H_2O$;
(b) 10 eq. MX, CH_3CN/CH_3COOH, and reflux, X=-N_3, -SCN

Figure 1.

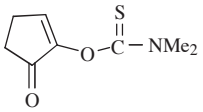
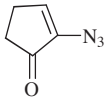
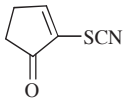
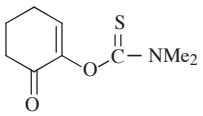
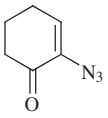
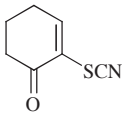
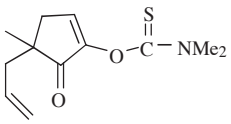
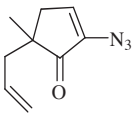
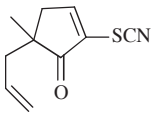
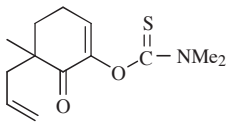
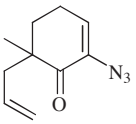
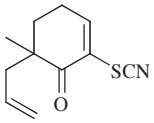
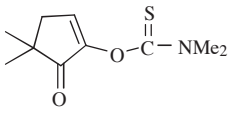
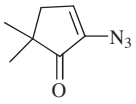
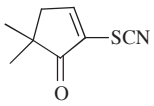
The structure of the replacement products of diosphenol thiocarbamates and the yields of the reactions are summarized in the Table.

Some other nucleophiles were examined using potassium cyanide and potassium cyanate to synthesize 2-cyano- and 2-cyanato-2,3-unsaturated ketones under similar conditions; however, none of the expected products were observed and only the starting diosphenol dimethyl thiocarbamates were recovered. We think that this was the result of an insufficient concentration of the nucleophile in the acetic acid-acetonitrile solvent system, due to poor solubility of the related salts.

The replacement of enolic oxygen with azide and thiocyanate may be mechanistically explained with the mechanistic postulates[2] shown in Figure 2.

In conclusion, several 2-azido- and 2-thiocyanato-2,3-unsaturated cyclic ketones were prepared starting from diosphenols. This is an important achievement since nucleophilic displacement at the unactivated sp^2 carbon is extremely difficult, even with very good leaving groups. High nucleophilicity of sulfur atoms in thioamides makes the addition of intramolecular conjugate to the protonated α,β-unsaturated carbonyl group in acidic conditions possible. The resulting product reacted with azides and thiocyanates to generate the corresponding products.

Table. Diosphenol thiocarbamates; their replacement products and yields.

Diosphenol Thiocarbamates	2-azido products	2-thiocyanato products
 **1b**	 **1c** (41%)	 **1d** (43%)
 **2b**	 **2c** (66%)	 **2d** (16%)
 **3b**	 **3c** (45%)	 **3c** (67%)
 **4b**	 **4c** (42%)	 **4d** (53%)
 **5b**	 **5c** (50%)	 **5d** (68%)

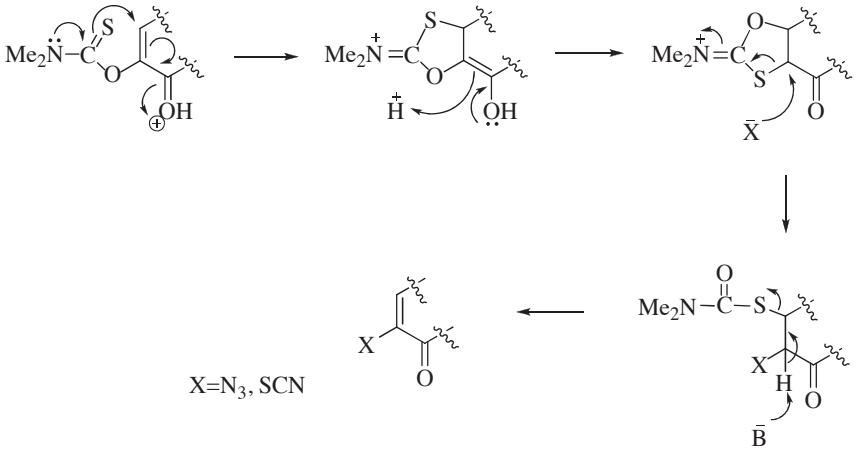


Figure 2.

Acknowledgement

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