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Hypervalent Iodine Oxidation of 5-Substituted and 4,5-Disubstituted Pyrazol-3(2*H*)-ones: A Facile Synthesis of Methyl-2-alkynoates and Methyl 2,3-alkadienoates

R. M. Moriarty, R. K. Vaid, V. T. Ravikumar, T. E. Hopkins and P. Farid
University of Illinois at Chicago
Department of Chemistry
P.O. Box 4348
Chicago, IL 60680

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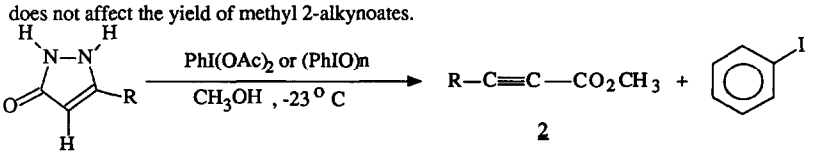
Summary: Hypervalent iodine oxidation of various 5-substituted pyrazol-3(2*H*)-ones (1a-h) with iodobenzene diacetate or iodosobenzene in methanol results in fragmentative loss of molecular dinitrogen to yield methyl 2-alkynoates (2a-h). However, 5-methyl-4-substituted pyrazol-3(2*H*)-ones (3a-d) under similar conditions yield methyl 2,3-allenic esters (4a-d). Methyl 2,3-cycloalkadienoates (6a-e) are obtained by the oxidative cleavage of 4,5-polymethylene pyrazol-3(2*H*)-ones (5c-e) using iodobenzene diacetate or iodosobenzene in methanol. 5-Methyl-4,4-disubstituted pyrazol-3(2*H*)-ones (7a-b) were found not to undergo reaction under similar conditions. The scope and mechanism of these reactions are discussed.

Methyl 2-alkynoates and methyl 2,3-alkadienoates are useful intermediates for the synthesis of a variety of complex acyclic, carbocyclic and heterocyclic molecules.[1,2] In recent years, many methods have been devised for their preparations[1,2] among which are the oxidation of pyrazole-3(2*H*)-ones by $Tl(NO_3)_3$[3-5] and $Pb(OAc)_4$[6]. Earlier, in a preliminary communication[7], we have reported that the oxidation of 5-substituted pyrazol-3(2*H*)-ones (3) with iodobenzene diacetate in methanol led to methyl 2-alkynoates (2) and methyl 2,3-alkadienoates (4) respectively. In continuation of our studies on the synthetic utility of hypervalent iodine[8], we herein describe fully the scope of these hypervalent iodine oxidations using iodobenzene diacetate or iodosobenzene in methanol.

Treatment of 1 equiv. of 5-substituted pyrazol-3(2*H*)-ones (1a-h) with 2 equiv. iodobenzene diacetate or iodosobenzene, in methanol, at -23°C gave methyl 2-alkynoates. The iodobenzene diacetate or iodosobenzene is reduced to iodobenzene(Scheme 1). The scope of this reaction is further defined by the observation that the nature of the C-5 substituent in the pyrazol-3(2*H*)-ones does not affect the yield of methyl 2-alkynoates.

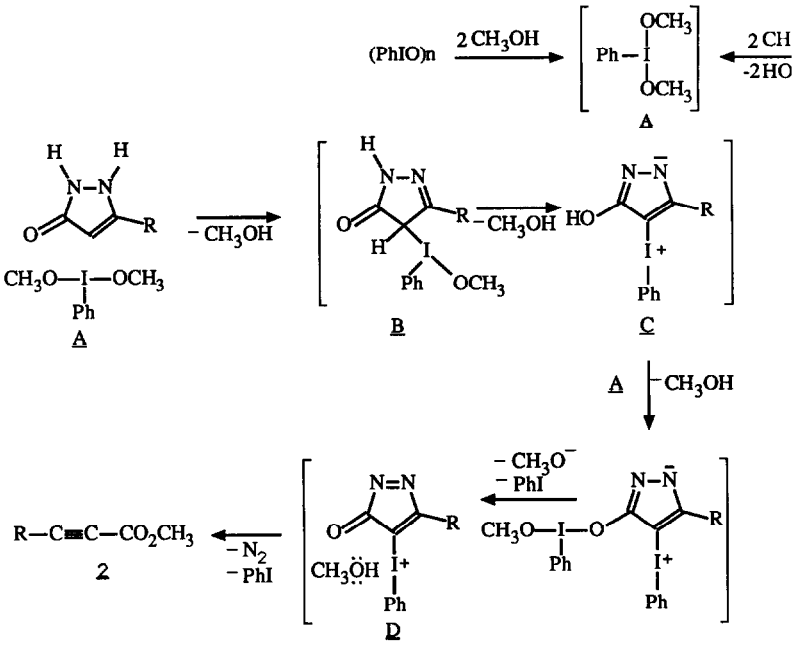


1 2

1 a, R = -CH_3 e, R = -C_6H_5
b, R = -CH_2CH_3 f, R = -C_6H_4Cl (p)
c, R = -$COOCH_3$ g, R = $C_6H_4CH_3$ (p)
d, R = -CH_2COOCH_3 h, R = -$C_6H_4OCH_3$ (p)

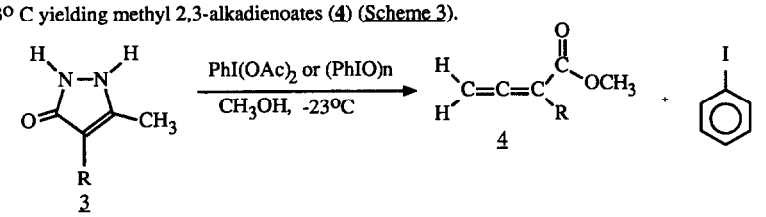
Scheme 1 (Yields range from 59 to 64 percent)

A plausible mechanism for the synthesis of methyl 2-alkynoates may be: i) generation of the tricoordinate species, (dimethoxyiodo)benzene A, either by the addition of methanol to iodosobenzene[9] or nucleophilic substitution by methanol in the case of iodobenzene diacetate; ii) electrophilic addition of A to the C-4 position of pyrazole to give intermediate B which then loses methanol to form an intermediate ylide C; (this type of ylide system is known for pyrazole[10]), iii) ligand transfer of a second molecule of A followed by reductive elimination of iodobenzene to form intermediate D iv) nucleophilic addition of methanol to the carbonyl carbon of D followed by a second reductive elimination with fragmentative loss of molecular dinitrogen to yield methyl 2-alkynoate (2) (Scheme 2)



Scheme 2

In a further study of this oxidation, 1 equiv. of 5-methyl-6-substituted pyrazol-3(2*H*)-ones (3) were treated with iodosobenzene diacetate (2 equiv.) or iodosobenzene (2 equiv.) in methanol at -23° C yielding methyl 2,3-alkadienoates (4) (Scheme 3).

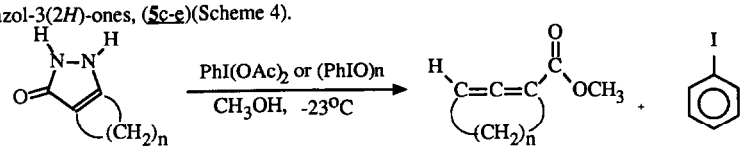


3,4, a, R = CH_3 3,4 c, R = CH_2COOCH_3

b, R = CH_2CH_3 d, R = $CH_2C_6H_5$

Scheme 3 (Yields range from 57 to 66 percent)

Encouraged by these transformations, the syntheses of the more difficultly accessible methyl 2,3-cycloalkadienoates (6c-e) were achieved in good yields by the oxidation of 5,4-polymethylene pyrazol-3(2*H*)-ones, (5c-e)(Scheme 4).



5 a, n = 5 6, c, n = 6

b, n = 6 d, n = 7

c, n = 7 e, n = 9

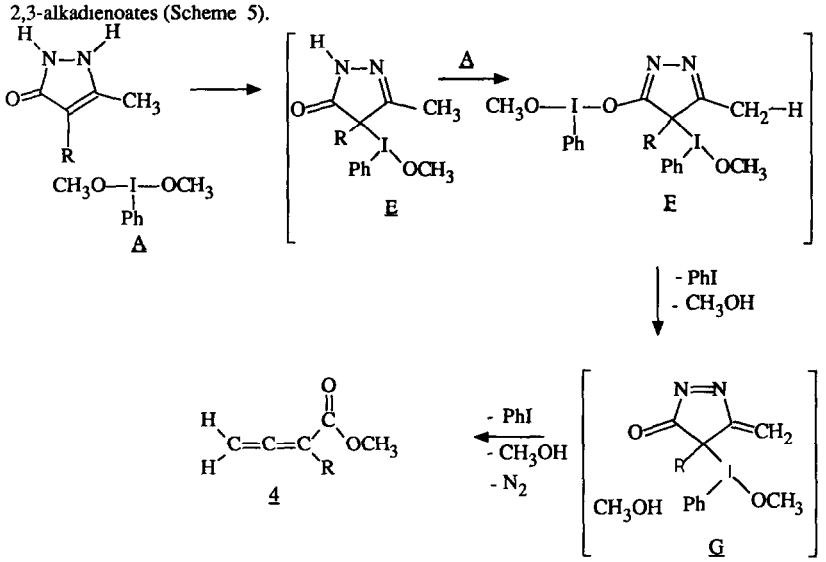
d, n = 8

e, n = 10

Scheme 4 (Yields range from 49 to 58 percent)

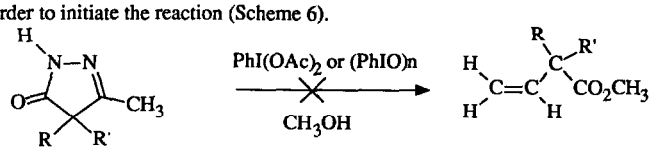
However, in the case of 4,5-cycloheptane pyrazol-3(2H)-one (5a) and 5,4-cyclooctane pyrazol-3(2*H*)-one (5b), the oxidations under similar conditions were unsuccessful and starting materials 5a and 5b were recovered . This may be due to the relatively small ring size of the starting pyrazol-3(2*H*)-ones (5a-b).

The formation of 4a-d and 6a-c may be explained by i) electrophilic addition of A to the C-4 position of the pyrazol to form intermediate E which due to C-4 substitution of pyrazol-3(2*H*)-ones (4a-d and 6c-e) cannot form an ylide, ii) intermediate E then undergoes addition of another molecule of A to give F, iii) which then undergoes reductive elimination of iodobenzene via the loss of a proton from the methyl or methylene group at the C-5 position of pyrazol to yield intermediate G. (This loss of a proton from F indicates that the presence of a methyl or methylene group at the C-5 position is necessary. This observation is confirmed by the fact that 5-aryl-4-substituted-pyrazol-3(2*H*)-ones do not undergo oxidation under these conditions and starting materials were recovered.) iv) The reaction is completed by the addition of methanol to G, followed by loss of molecular dinitrogen and reductive elimination of iodobenzene to yield methyl 2,3-alkadienoates (Scheme 5).



Scheme 5

When 5-methyl-4,4-disubstituted pyrazol-3(2*H*)-one (7a-b) were treated with iodobenzene diacetate or iodosobenzene in methanol at room temperature or -23° C, there was no formation of olefinic esters (8a-b) observed. Rather, starting materials were recovered. The reason for this behavior may be due to the fact that the C-4 position is disubstituted and hyperiodination cannot occur in order to initiate the reaction (Scheme 6).



7 8

7,8,a, R = R' = CH3

b, R = R' = Cl

Scheme 6

This method of hypervalent iodine oxidation of pyrazol 3(2H)-ones to methyl 2-alkynoates and methyl 2,3-alkadienoates is advantageous because the yields are good, the reaction conditions are mild and the inconvenient toxicity of thallium and lead reagents are avoided.

Experimental

Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained using an IBM system 9000 IR/32 spectrophotometer and peak positions are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded at 60 MHz with a Varian EM 360-L spectrometer using $SiMe_4$ as an internal standard. Mass spectra were obtained using a Hewlett Packard GC/MS 5985 apparatus at 70 eV.

Starting materials: Iodobenzene diacetate, hydrazine hydrate and β-ketoesters (required for the synthesis of 1a-h, 3a-d, 5a) were obtained from Aldrich and Co. 2-Carbomethoxycycloalkanones required for the synthesis of 5b-e were prepared by the method of Rhoads[11] involving carbomethoxylation of appropriate cyclic ketone by dimethyl carbonate and sodium hydride. Following the literature procedure[12], the synthesis of 5-substituted pyrazol-3(2*H*)-ones (1) and 5-methyl-4-substituted pyrazol-3(2*H*)-ones (3) was achieved using hydrazine hydrate and appropriate β-ketoester. 3,4-Polymethylene pyrazol-3(2*H*)-ones (5) were prepared according to the method of Silveira et al.[6] 5-Methyl-4,4-dimethylpyrazol-3(2*H*)-one (7a) and 5-methyl-4,4-dichloropyrazol-3(2*H*)-one (7b) were prepared according to literature procedure.[13]

General Procedure for the Preparation of Methyl-2-alkynoate (2a-h)

A methanolic solution (40 mL) of 5-substituted pyrazol-3(2*H*)-one (1, 0.01 mol) was added to a stirred methanolic solution of iodobenzene diacetate or iodosobenzene, cooled to -23 °C, over a 45 minute period. The mixture was stirred for an additional 1 hr at room temperature. The solvent was reduced *in vacuo* to one-third volume and the resulting solution was diluted with water (neutralized with saturated aqueous sodium hydrogen carbonate in case of iodobenzene diacetate) and extracted with dichloromethane (4 X 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield the crude product and iodobenzene. Pure products were obtained either by column chromatography (hexane and ether as eluents) or by reduced pressure distillation.

Compounds thus obtained are:

Methyl 2-butynoate (2a): % yield = 60, bp = 82-85°C/85mm, [Lit.][14]bp = 80-82° C /85mm, IR (Neat) cm^{-1}: 1720 (sh, C=O stretching); 2210 (sh, - C ≡ C - stretching); ^{1}H-NMR (CDCl 2.0 (s, 3H, CH_3), 3.75 (s, 3H, $COOCH_3$).

Methyl 2-pentynoate (2b): % yield = 63, oil, (purified by column chromatography [Lit.][5] bp = 72°C/10 mm. IR (Neat) cm^{-1}: 1720 (sh, C=O stretching); 2190 (sh, - C ≡ C -, stretching); ^{1} NMR (CDCl)3 δ: 1.25 (t, 3H, -CH_2CH_3), 2.3 (q, 2H, CH_2CH_3), 3.8 (s, 3H, $COOCH_3$).

Dimethyl acetylenedicarboxylate (2c): % yield = 59, bp = 92-95°C/19 mm, [Lit.][16] bp = 95-98° C/19 mm, IR (Neat) cm^{-1}: 1720 (br, C=O stretching), 2210 (sh, - C ≡ C - stretching); ^{1}H-NI (CDCl3) δ: 3.8 (s, 6H, 2 X $COOCH_3$).

Methyl (3-methylcarboxymethyl)propynoate (2d): % yield = 62, oil (purified by column chromatography) [Lit.][17] bp = 90-92°C/4mm, IR (Neat) cm^{-1}: 1730 (br, C=O stretchings), 2220 (sh, -C ≡ C- stretching); ^{1}H NMR (CDCl3) δ: 3.4 (s, 2H, CH_2), 3.75 (s, 3H, $COOCH_3$), 3.8 (s, C ≡ C-$COOCH_3$).

Methyl 3-phenylpropynoate (2e): % yield = 59, bp = 95-96°C/1mm, [Lit.][18]bp = 128° C/4mm, IR cm^{-1}: 1720 (sh, C=O stretching), 2110 (sh, -C ≡ C- stretching); ^{1}H-NMR (CDCl3) δ: 3.8 3H, $COOCH_3$), 7.2-7.6 (m, 5H, aromatic protons).

Methyl 3-(p-chlorophenyl)propynoate (2f): % yield = 61, mp 90-91°C, [Lit.][18] mp = 92-94°C, IR cm^{-1}: 1720 (sh, C=0 stretching), 2226 (sh, -C ≡ C- stretching), ^{1}H- NMR (CDCl3) δ: 3 3H, $COOCH_3$), 7.3 (d, 2H, aromatic protons), 7.7 (d, 2H, aromatic protons).

Methyl 3-(p-methylphenyl)propynoate (2g): %yield=59, m.p.=67-69°C, [Lit.][18] mp.=68-70°C, IR (KBr) cm^{-1}: 1725 (sh, C=O stretching), 2210 (sh, - C ≡ C - streching), ^{1}H-NMR ($CDCl_3$) δ : (S, 3H, CH_3), 3.8 (S, 3H, $COOCH_3$), 7.2-7.6 (q, 4H, aromatic protons).

Methyl 3-(p-methoxyphenyl)propynoate (2h): % yield = 64; mp = 45-47° C [Lit.][18]mp = 45-47° C, IR (KBr) cm^{-1}:L 1725 (sh, C=O stretching), 2226 (sh, -C ≡ C-, stretching); ^{1}H-N ($CDCl_3$) δ : 3.9 (s, 3H, $COOCH_3$), 3.95 (s, 3H, OCH_3), 7.0 (d, 2H, aromatic protons), 7.7 (d, 2H aromatic protons).

General Procedure for the Preparation of Methyl 2,3-alkadienoates (4a-d, 6a-e)

5-Methyl-4-substituted pyrazol-3(2*H*)-ones (3) (0.01 mole) or 5,4-polymethylene pyrazol-3(2*H*)-ones (5) (0.01 mol) was dissolved in 40 mL of methanol. This solution was added to a stirred solution of 0.02 mol of iodobenzene diacetate or iodosobenzene dissolved in 50 mL of methanol cooled at -23° C over 40 minutes. After the addition, stirring was continued for an additional 2 hours at room temperature. The volume of methanol was reduced *in vacuo* to one-third. The resulting solution was diluted with water (neutralized with saturated aqueous sodium hydrogen carbonate in case of iodobenzene diacetate) and extracted with dichloromethane (5 X 100 mL). The combined dichloromethane layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude products (4) and (6), respectively, with iodobenzene. Products were purified either by column chromatography (using hexane:ether as the eluent) or by reduced pressure distillation.

Compounds thus obtained are:

Methyl 1-methyl-2,3-butadienoate (4a): % yield = 64, oil (purified by column chromatography), IR (Neat) cm^{-1}: 1728 (sh, C=O stretching), 1969 (br, C=C=C stretching); ^{1}H-NMR ($CDCl_3$) δ 1.90 (t, 3H, CH_3), 3.74 (s, 3H, $COOCH_3$), 5.1 (t, 2H, C=C=CH_2).

Methyl 1-ethyl-2,3-butadienoate (4b): % yield = 64, bp = 60-62°C/11 mm, [Lit.][6] bp = 60-62°C/11 mm, IR (Neat) cm^{-1}: 1730 (sh, C=O stretching), 1975 (br, C=C=C stretching); ^{1}H-NMR ($CDCl_3$) δ : 1.05 (t, 3H, CH_2CH_3), 2.1 (m, 2H, CH_2CH_3), 3.70 (s, 3H, $COOCH_3$), 5.1 (t, 2H C=C=CH_2).

Methyl 1-methylcarboxymethyl-butadienoate (4c): % yield = 57, oil (purified by column chromatography), IR (Neat) cm^{-1}: 1735 (br, C=O stretching), 1964 (br, C=C=C stretching); ^{1}H-NMR ($CDCl_3$) δ : 3.3 (dd, 2H, =C-CH_2COOCH_3), 3.75 (s, 3H, $COOCH_3$), 3.75 (s, 3H $COOCH_3$), 5.1 (dd, 2H, H_2C=C=C); $C_8H_{10}O_4$ requires % C = 56.44, H = 5.9 Found % C = 56.20, H = 5.7.

Methyl 1-benzyl-2,3-butadienoate (4d): % Yield = 66, bp 114-116°C/0.04 mm, IR (Neat) cm^{-1}: 1750 (br, C=O stretching), 1970 (br, C=C=C stretching); ^{1}H-NMR ($CDCl_3$) δ : 3.6 (m, 2H, =C CH_2Ph), 3.75 (s, 3H, $COOCH_3$), 5.1 (t, 2H, C=C-CH_2), 7.1-7.4 (m, 5H, aromatic protons). $C_{12}H_{12}O_2$ requires (%) C = 76.6, H = 6.38; Found (%) C = 76.3, H = 5.96.

Methyl 2,3-cyclononadienoate (6c): % yield = 49, oil (purified by column chromatography), IR (Neat) cm^{-1}: 1714 (br, C=O stretching), 1973 (br, C=C=C stretching), ^{1}H-NMR ($CDCl_3$) δ : .95 - 2.60 (m, 12H, -$(CH_2)_6$-), 3.73 (s, 3H, -O-CH_3), 5.74 (m, 1H, HC=C=C)

Methyl 2,3-cyclodecadienoate (6d): % yield = 58, oil (purified by column chromatography), IR (Neat) cm^{-1}: 1725 (br, C=O stretching), 1965 (br, C=C=C stretching); ^{1}H-NMR ($CDCl_3$) δ : .95 - 2.55 (m, 14H, -$(CH_2)_7$-), 3.76 (s, 3H, $COOCH_3$), 5.56 (m, 1H, HC=C=C)

Methyl 2,3-cyclododecadienoate (6e): % yield = 56, oil (purified by column chromatography), IR (Neat) cm^{-1}. 1725 (br, C=O stretching), 1963 (br, C=C=C stretching); ^{1}H-NMR ($CDCl_3$) δ : .95 - 2.60 (m, 18H, -$(CH_2)_9$-), 3 68 (s, 3H, $COOCH_3$), 5.37 (m, 1H, HC=C=C)

Compounds 6c, 6d, and 6e IR and ^{1}H-NMR spectral characteristics are identical to reported values.[5]

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