Thermal Rearrangement of α-Oxo-α,β-unsaturated Azines to N-Substituted Pyrazoles

Thomas A. Albright, Steven Evans,[1] Choong S. Kim, Clifford S. Labaw, Andrea B. Russiello,[1] and Edward E. Schweizer*

Department of Chemistry, University of Delaware, Newark, Delaware 19711.

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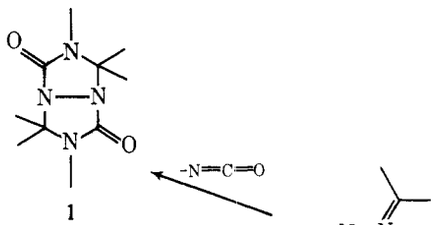
Thermolysis of α-oxo-α,β-unsaturated azines (**9**) was found to be an efficient and general route to α-pyrazolyl esters (**12**, R_1 = OEt) or ketones (**12**, R_1 = alkyl or aryl). The azines were readily synthesized by either the condensation of α-diketone monohydrazones (**22**, **25**) with α,β-unsaturated aldehydes and ketones (**26**) or the Wittig olefination of the stabilized phosphoranes (**17**, **18**) with aryl adehydes.

We would like to report a simple, general synthesis of the pyrazole ring system based on the thermolysis of α-oxo-α,β-unsaturated azines **9** (Scheme I). Although azines (e.g., **3**) are dienes, the 1,3 relationship of an eletrophillic C–N double bond and a relatively electron-rich nitrogen greatly alters the cycloaddition behavior of these compounds. Attempted



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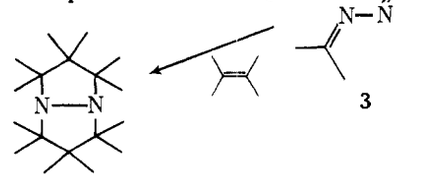

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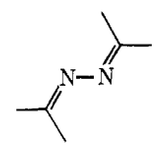

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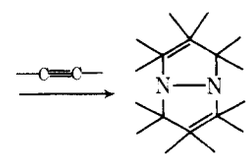

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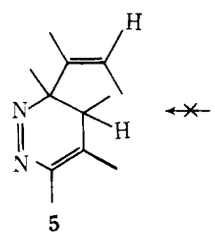

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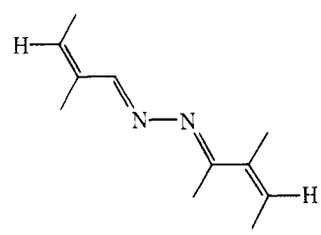

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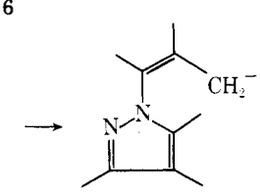

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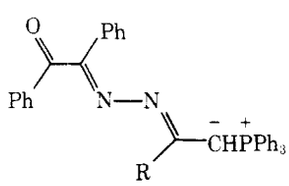
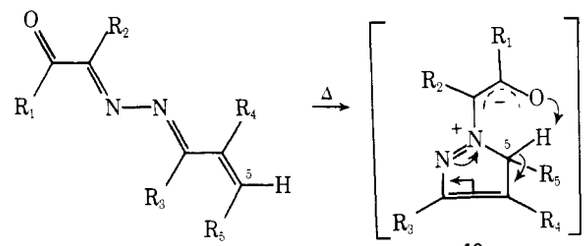


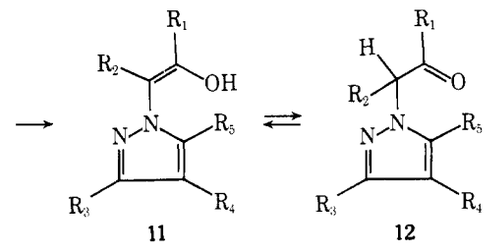
8a, R = CH_3

b, R = $Ph_3\overset{+}{P}\overset{-}{C}H$–

Scheme I



9 **10**

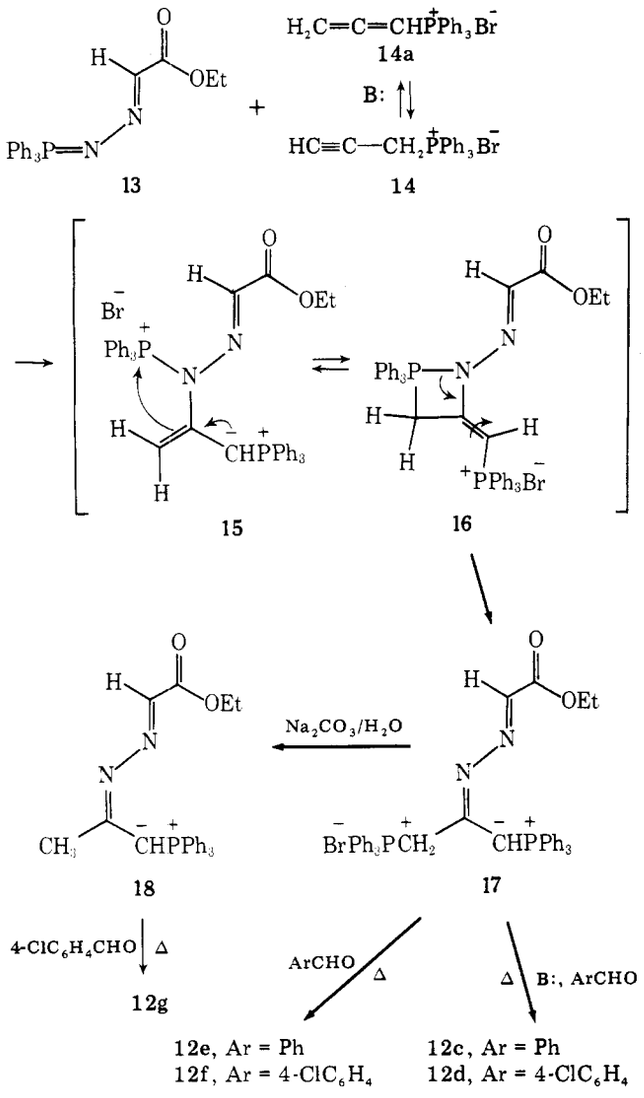


11 **12**

	R_1	R_2	R_3	R_4	R_5
9–12a,	Ph	H	4-ClC_6H_4CH=CH–	H	4-ClC_6H_4
b,	Ph	H	CH_3	H	4-ClC_6H_4
c,	EtO	H	PhCH=CH–	H	Ph
d,	EtO	H	4-ClC_6H_4CH=CH–	H	4-ClC_6H_4
e,	EtO	H	$Br\overset{-}{P}h_3\overset{+}{P}CH_2$–	H	Ph
f,	EtO	H	$Br\overset{-}{P}h_3\overset{+}{P}CH_2$–	H	4-ClC_6H_4
g,	EtO	H	CH_3	H	4-ClC_6H_4
h,	Ph	Ph	CH_3	H	4-ClC_6H_4
i,	CH_3	CH_3	H	H	Ph
j,	Ph	Ph	H	H	Ph
k,	Ph	Ph	H	H	
l,	Ph	Ph	H	H	CH_3
m,	Ph	Ph	H	CH_3	Ph
n,	Ph	Ph	CH_3	H	Ph
o,	Ph	Ph	CH_3	H	
p,	Ph	Ph	Ph	H	Ph
q,	Ph	Ph	Ph	H	–COPh
r,	Ph	Ph	H	Br	Ph
s,	Ph	Ph	H	$-CH_2CH_2CH_2CH_2-$	
t,	Ph	Ph	H	$-CH_2CH_2CH_2O-$	
u,	Ph	Ph	H	$-CH_2OCH_2CH_2-$	
v,	Ph	Ph	H	$-CH_2CH_2CH_2-$	
w,	Ph	Ph	$-CH_2CH_2CH_2CH_2-$		Ph
x,	Ph	Ph	$-CH_2CH_2CH_2-$		Ph

Diels–Alder reaction of azines with olefins, isocyanates, or acetylenes leads[2,3] to bicyclic 2:1 (dienophile/azine) adducts **1**, **2**, or **4** (or products of further thermal rearrangements[2,3]), respectively, rather than the expected 1:1 adducts associated with butadienes. This type of reactivity is unique to azine chemistry and has been termed[2] "criss-cross" cycloaddition.

Scheme II

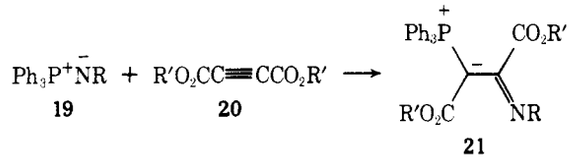


Azines (6) derived from α,β-unsaturated aldehydes and ketones exhibited[4,5] similar intramolecular cycloaddition reactivity, yielding *N-cis*-propenylpyrazoles **7**, rather than cyclic azo compounds **5**, on thermolysis.

Recently we reported[6] that stabilized phosphoranes **8a** and **8b** yielded phenacyl pyrazoles, **12a** and **12b** (Scheme I), when allowed to react with benzaldehyde. Presumably, the origin of these products was a thermal rearrangement of azines **9a** and **9b** (the expected Wittig olefination products) similar to that observed for **6**. Scheme I outlines a proposed mechanism for this rearrangement based on the work of Stern and Krause.[4,5] Initial attack of the imine nitrogen on the terminal olefinic carbon of **9** would generate the azomethine imine **10**. A prior isomerization of one or both of the C–N double bonds in **9** may be necessary in order to attain the correct geometry for the cyclization (**9** → **10**). If the original azine **9** was mono- or unsubstituted at C-5, aromatization by intramolecular hydrogen transfer could occur, leading to the observed products. Any azine of the type **9**, bearing at least one hydrogen substituent on C-5, should serve as a precursor for pyrazoles **12** (and/or **11**), making the overall sequence an attractive new route to N-substituted pyrazoles. We now wish to report our investigations into the synthetic utility of these transformations.

Results and Discussion

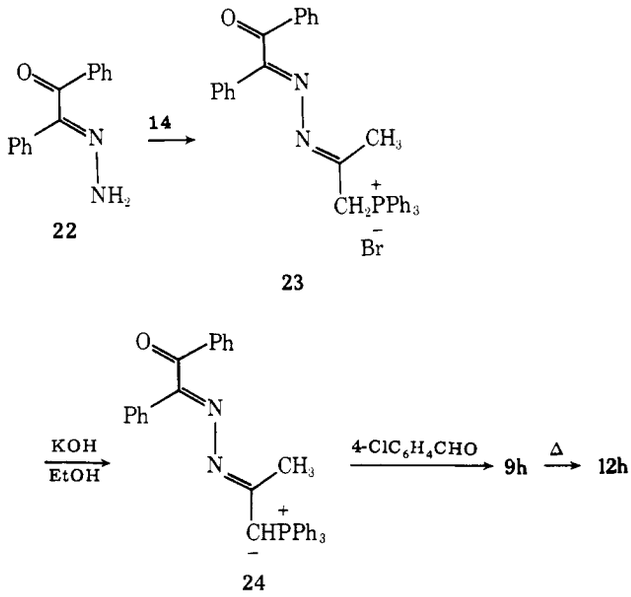
Syntheses of Azines and Pyrazoles Based on Phosphonium Ylide Intermediates. Ylide salt **17** may be readily synthesized by the reaction of carboethoxyphophazine (**13**) with propargyltriphenylphosphonium bromide (**14**) (Scheme II). Brown[7] has reported an analogous reaction, yielding phosphoranes (**21**) from phosphinimines (**19**) and acetylenic



esters (**20**). The formation of **17** probably involved the series of steps outlined in Scheme II. Initial reaction of **13** with the allenyl isomer (**14a**) of **14**[8] would yield zwitterion **15**, presumably in equilibrium with azaphosphetidine **16**. Decomposition of **16** in the indicated manner would then generate **17**.

After treatment with a strong base (NaH or NaOEt, forming a bisylide) **17** could be converted in good yield to pyrazoles **12c** or **12d** by reaction with benzaldehyde or 4-chlorobenzaldehyde, respectively. Simply heating **17** in the prescence of the same aldehydes led to **12e** or **12f**, which retain the methylenetriphenylphosphonium moiety. Mild alkaline hydrolysis (Na_2CO_3, H_2O) of **17** selectively cleaved one of the triphenylphosphonium substituents, yielding ylide **18**, which could in turn be converted to pyrazole **12g** by heating with 4-chlorobenzaldehyde. Elemental and spectral analysis of the colorless crystalline products **12c–g** supports the structural assignments (see Tables III and IV). The configuration of the 3-styryl groups in **12a**, **12c**, and **12d** could not be determined since, in the ^1H NMR, the vinyl protons were obscured by aromatic resonances.

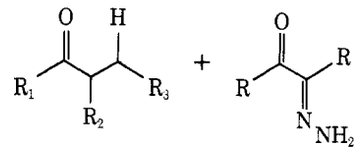
Azines **9a–g** were presumably intermediates in these reactions, although they were not isolable under the reaction conditions. The intermediacy of **9** in a related system was confirmed. Azine phosphonium salt **23** could be readily prepared by employing the reaction of benzil monohydrazone (**22**)



with propargylphosphonium salt **14**. When the corresponding ylide (**24**) was allowed to react with 4-chlorobenzaldehyde, an orange solid resulted which could be converted to colorless pyrazole **12h** by distillation at 260 °C (0.5 mm). This sequence, coupled with an analysis of its spectral data, allows us to assign the structure of the orange solid as azine **9h**.

Syntheses of Azines and Pyrazoles From α-Diketone Monohydrazones and α,β-Unsaturated Carbonyl Compounds. Intermediates based on phosphonium salt **14** were useful synthons for a number of pyrazole systems (i.e., **12a–h**), but limited the substituents which could be introduced into

Table I. Reactions of α-Diketone Monohydrazones with α,β-Unsaturated Aldehydes and Ketones



22, R = Ph
25, R = CH_3

	R_1	R_2	R_3	Hydrazone	Product	Yield,[a] %	Method[b]
26a	H	H	Ph	25	9i	68	B, 4 h
a	H	H	Ph	22	9j	86	A, 24 h
b	H	H	2-Furyl	22	9k	52	A, 4 h, *p*-TSA[c]
c	H	H	CH_3	22	12l	50	A, 12 h
d	H	CH_3	Ph	22	12m	91	A, 25 h, HOAc
e	CH_3	H	Ph	22	12n	75	A, 24 h, *p*-TSA
f	CH_3	H	2-Furyl	22	12o	48	A, 5 h, *p*-TSA
g	Ph	H	Ph	22	12p	57	A, 8 h, *p*-TSA
h	Ph	H	COPh	22	12q	54	A, 8 h, *p*-TSA
i	H	Br	Ph	22	9r	82	A, 3.5 h
j	H	$-CH_2CH_2CH_2CH_2-$		22	9s	79	A, 5 h, HOAc
k	H	$-CH_2CH_2CH_2O-$		22	9t	38	B, 7 h
l	H	$-CH_2OCH_2CH_2-$		22	9u	82	A, 5 h, HOAc
m	H	$-CH_2CH_2CH_2-$		22	9v	83	A, 5 h, HOAc
n	$-CH_2CH_2CH_2CH_2-$		Ph	22	12w	62	A, 19 h, *p*-TSA
o	$-CH_2CH_2CH_2-$		Ph	22	9x	75	A, 36 h, *p*-TSA

[a] Isolated yield based on hydrazone. [b] See Experimental Section. [c] *p*-Toluenesulfonic acid.

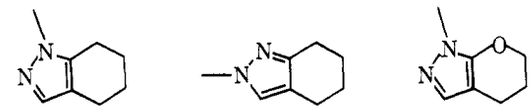
Table II. Thermolysis of Azines

Azine	Conditions (*T*, °C/time, h)	Product(s)	% yield
9i	180/1	**12i**	90
9j	175/2	**12j**	88
9k	130/2.5	**12k**	64
9r	175/2.5	**12r**	67
9s	150/4	**12s**	72
9t	175/3	**11t**	74
9u	150/5	**12u**	85
9v	150/4	**12v**	73
9x	160/4	**11x**	25
		12x	50

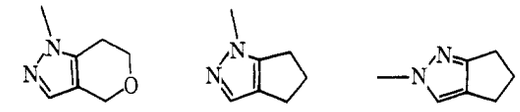
the heterocyclic ring. Thus, we sought a more general route to α-oxo-α,β-unsaturated azines **9** utilizing readily available starting materials. We reasoned that the reactions of α-diketone monohydrazones (**22** or **25**) with α,β-unsaturated aldehydes or ketones (**26**) would provide a flexible and straightforward route to azines **9** and/or their rearrangement products (**11/12**) (see Table I).

In fact, when cinnamaldehyde (**26a**) was allowed to react with either diacetyl (**25**) or benzil (**22**) monohydrazone, azines **9i** and **9j** could be isolated in good yield. We have extended this sequence to include the reactions of **22** with a variety of other α,β-unsaturated aldehydes and ketones (**26b–p**), summarized in Table I. Azines (**9**) were isolable in approximately half of the reactions, pyrazoles, **11**, and/or **12**, being formed directly in the remainder. The α-oxo-α,β-unsaturated azines, ranging in color from yellow to orange, could be converted to the colorless pyrazoles **11/12** in good yield by thermolysis (Table II). Although no attempts at optimization were made, the yields were generally good (38–91%), establishing this reaction sequence (**22/25** + **26** → **9** → **11/12**) as a viable route to α-pyrazolyl ketones.

In addition to monocyclic pyrazoles (**12i–r**), this sequence permitted the synthesis of bicyclic systems when the carbonyl or olefinic portion of **26** was incorporated into a carbo- or heterocyclic ring. By proper choice of the α,β-unsaturated aldehyde or ketone (**26**) we were able to prepare examples of the 1*H*- (**A**) and 2*H*-tetrahydroindazole (B) (**12s** and **12w**),



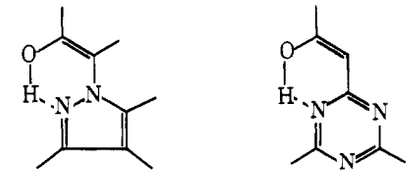
A B C



D E F

pyrazolo[5,4-*b*]-(C) and pyrazolo[4,5-*c*]pyran (D) (**11t** and **12u**), and 1*H*- (E) and 2-*H*-cyclopentapyrazole (F) (**12y** and **11x/12x**) systems.

Interestingly, in two cases, enol tautomers (**11t** and **11x**) of the α-pyrazolyl ketones were isolable. The infrared spectra were particularly distinctive, showing bands for OH (~3450 cm^{-1}) and C=C (~1570 cm^{-1}), while lacking a carbonyl stretching absorption. Additional support was provided by the conversion of pure **11x** to a mixture (as determined by thin-layer chromatography) of **11x** and **12x** upon heating at 170 °C for 2 h. Presumably stabilization of the enol form in these cases is provided by intramolecular hydrogen bonding with N-2 of the pyrazole ring as in **27**. Similar enol stabilization is seen in α-triazinyl ketones (e.g., **28**).[9] We can offer no explanation as to why these two systems were the only ones in which the enol was isolable.



27 **28**

Spectral Characteristics. Table III lists the physical properties and characteristic IR absorption frequencies of the azines and pyrazoles described above. Azines **9** exhibit bands at 1665–1685 (conjugated C=O) and 1570–1625 cm^{-1} (C=N, C=C) in their infrared spectra. The α-pyrazolyl esters **12c–g** show strong bands at ~1750 (ester C=O) and ~1590 cm^{-1}

Table III. Physical Properties and Characteristic Infrared Bands of Azines (9) and Pyrazoles (11/12)

Compd	Mp[a] (bp/mm), °C	IR[b] cm^{-1}
9h	117–118	1685, 1595, 1575
9i	67.5–69	1680, 1625, 1545
9j	133.5–135	1675, 1620, 1580
9k	106–108	1665, 1615, 1580
9r	145–146	1660, 1595, 1565
9s	100–101	1675, 1630, 1590
9t	89–91	1665, 1620, 1590
9u	134.5–136	1675, 1640, 1595
9v	81–82	1680, 1620, 1590
9x	157–158	1675, 1595, 1575
11t	126–128	3450, 1560, 1525
11x	165.5–167	3460, 1560, 1530
12c	87–89	1750, 1580
12d	139–140	1750, 1600
12e	208–209	1740, 1570
12f	175–176	1740, 1580
12g	64–65	1750, 1600
12h	151–152	1700, 1600
12i	(100/1.1)	1730, 1610
12j	129–130	1705, 1600
12k	145	1690, 1600
12l	151.5–152.5	1690, 1595
12m	137.5–138.5	1700, 1600
12n	105–106.5	1690, 1595
12o	138–139	1665, 1615, 1570
12p	110	1690, 1600, 1580
12q	119–121	1680, 1630, 1575
12r	140–141	1665, 1590
12s	123–124	1695, 1600
12u	139.5–140.5	1695, 1600
12v	146–147	1680, 1600
12w	120–122	1700, 1600
12x	133–134.5	1690, 1595

[a] Melting (boiling) points are uncorrected. [b] Standarized by reference to polystyrene film.

(pyrazole C=N/C=C).[10] Infrared spectra of α-pyrazolyl ketones **12h–s** and **12u–x** are characterized by peaks at 1690–1730 (C=O) and ~1600 cm^{-1} (pyrazole C=N/C=C).

Proton NMR data for all compounds are collected in Table IV and are completely consistent with the assigned structures. A few general observations may be made. The aldimine (**HC**=N–) protons in those azines derived from aldehydes (**9i,j,k** and **9r–y**) resonate at 7.8–8.2 ppm. In the pyrazole derivatives, systems unsubstituted at carbon 3 and/or 4 exhibit signals at 7.0–7.8 [C(3)–H] and/or 5.9–6.3 ppm [C(4)–H], consistent with reported[11] NMR data. In addition, the α-pyrazolyl α-phenyl ketones derived from benzil monohydrazone (**22**) and **26** show a characteristic peak at 6.4–7.0 ppm for the proton α to the carbonyl [C(2)–H].

Table V lists selected ^{13}C NMR parameters for the azines and pyrazoles synthesized by the α-diketone hydrazone–unsaturated aldehyde/ketone route. Peaks at 197–199 (C=O) and 160–170 ppm (C=N) as well as the lack of any saturated carbon resonances other than expected for aliphatic substituents characterize the spectra of the azines **9**. Enols **11t** and **11x**, as expected, show no peaks attributable to a carbonyl carbon, but the spectra do show a very deshielded (170–176 ppm) and a very shielded (~80 ppm) vinyl carbon, consistent with other reports[12] of the ^{13}C spectra of enols and enol ethers. The α-phenyl α-pyrazolyl ketones **12j–s** and **12u–x** show peaks at 104–117 [C(4)],[13] 192–194 [C(1)], and 67–69 ppm [C(2)]. The remainder of the resonances are consistent with the proposed structures and assignments are based on model compounds when available (e.g., ref 13).

We have demonstrated that the thermal rearrangement of α-oxo-α,β-unsaturated azines **9** is a facile and general route to N-substituted pyrazoles **11** and/or **12**, and should prove to be a valuable addition to current methods of pyrazole synthesis.

Experimental Section

All chemicals, except as noted below, were purchased from the Aldrich or Eastman Organic Chemical Companies and used as is. Solvents used in the phosphonium ylide reactions were dried by standard techniques and distilled prior to use. A dry nitrogen atmosphere was employed in all reactions. Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. Proton NMR spectra were recorded with either a Varian A-60A or Perkin-Elmer R12-b instrument on ~10% $CDCl_3$ solutions. A Bruker HFX-90 NMR spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system operating at 22.63 MHz was used to collect the ^{13}C NMR data. All NMR chemical shifts are reported as parts per million δ vs. Me_4Si as internal standard. All new compounds gave elemental (C, H) analyses consistent with the proposed empirical formulas.

Cyclcohexene-1-carboxyaldehyde (26j) was prepared by the method of Heilbron et al.[20] with the modification that triethylamine at 110–120 °C (pressure bottle) was used to effect the dehydrobromination. The following compounds were prepared by known methods: **propargyltriphenylphosphonium bromide (14),**[14] **ethyl (triphenylphosphoranylidenehydrazono)acetate (13),**[15] **2*H*-3,4-dihydropyran-5-carboxyaldehyde (26k),**[16] **cyclopentene-1-carboxyaldehyde (26m),**[17] **2-benzylidenecyclohexanone (26n),**[18] **2-benzylidenecyclopentanone (26o),**[18] and **diacetyl monhydrazone (25).**[19]

Preparation of 3-(Triphenylphosphoranylidene)-2-(carboethoxymethylidenehydrazonopropyl)triphenylphosphonium Bromide (17). A solution of 10.2 g (0.0266 mol) of propargyltriphenylphosphonium bromide (**14**) and 10.0 g (0.0266 mol) of phosphazine **13** in 200 mL of cold (0 °C), dry CH_2Cl_2 was stirred under nitrogen for 3 days at 0 °C and 2 days at room temperature. Addition of the reaction mixture to 1200 mL of EtOAc yielded **17** as a yellow powder. Recrystallization from CH_2Cl_2/EtOAc afforded 13.5 g (67%) of analytically pure material, mp 224.5–225.0 °C: IR (cm^{-1}) 1680 (C=O), 1580 (C=N), 1440, 1105 (C–P); ^1H NMR δ 0.6–1.5 (m, 3 H, CH_3CH_2O–), 3.50–4.50 (m, 3 H, CH_3CH_2O– + Ph_3P=CH–), 5.12 (d, J_{PH} = 15.0 Hz, $Ph_3{}^+CH_2$), 7.0–8.1 (m, 30 H, aromatic).

Anal. Calcd for $C_{43}H_{39}BrN_2O_2$: C, 68.16; H, 5.19. Found: C, 68.11; H, 5.15.

Preparation of Ethyl 1-(3-Styryl-5-phenylpyrazolyl)acetate (12c). In 60 mL of dry CH_3CN was dissolved 4.0 g (5.2 mmol) of ylide salt **17** and 1.4 g (14.4 mmol) of benzaldehyde. To this solution was added 0.24 g (0.05 mol) of sodium hydride (57% oil dispersion), and the reaction mixture was heated at reflux for 18 h. After cooling to room temperature, the reaction mixture was poured into water (500 mL) and extracted with two 150-mL portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to an oily solid. Column chromatography (silica gel; 1:1 hexane–ether as eluent) yielded 1.0 g (87%) of **12c** as a pale yellow solid. An analytical sample was prepared by crystallization from hexane–ether.

Preparation of Ethyl-1-[3-(4-chlorostyryl)-5-(4-chlorophenyl)pyrazolyl]acetate (12d). In 80 mL of freshly distilled ethanol was dissolved 0.46 g (0.02 mol) of sodium metal. Then 5.6 g (0.04 mol) of 4-chlorobenzaldehyde and 15.0 g (0.02 mol) of ylide salt **17** were added, and the reaction mixture was stirred at ambient temperatures for 5 h and at reflux for 72 h. The reaction was then poured into water (500 mL) and extracted with two 250-mL portions of ether; the ether extracts were dried ($MgSO_4$) and concentrated in vacuo to ~100 mL, at which point a solid precipitated. The solid (presumably Ph_3PO) was removed by filtration, the filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (1:1 ether–pentane as eluent), yielding 5.0 g (61%) of **12d** as a colorless solid. Recrystallization from ether–hexane afforded an analytical sample.

Preparation of Triphenyl-1-carboethoxymethyl-5-phenylpyrazol-3-ylmethylphosphonium Bromide (12e). A solution of 2.5 g (0.0033 mol) of ylide salt **17** and 0.70 g (0.0066 mol) of benzaldehyde in 200 mL of acetonitrile was heated at reflux for 29 h. After concentration in vacuo to 20 mL, the reaction mixture was precipitated into 700 mL of anhydrous ether, yielding 3.4 g (88%) of **12e** as a cream colored solid. An analytical sample was prepared by recrystallization from CH_2Cl_2–EtOAc.

Preparation of Triphenyl-1-carboethoxymethyl-5-(4-chlorophenyl)pyrazol-3-ylmethylphosphonium Bromide (12f). A solution of 5.0 g (0.066 mol) of ylide salt **17** and 1.86 g (0.0132 mol) of 4-chlorobenzaldehyde in 200 mL of acetonitrile was heated at reflux

Table IV. ^{1}H NMR Parameters for Azines (9) and Pyrazoles (11/12)[a]

9h 2.22 (s, 3 H, C(3)-CH_3), 6.62 ("d", $J \cong 6$ Hz, 2 H, C(4)-H + C(5)-H), 7.03 (s, 4 H, C_6H_4Cl), 7.2 (m, 6 H, aromatic), 7.70 (m, 4 H, aromatic ortho to C=O/C=N)

9i 2.01 (s, 3 H, C(2)-CH_3), 2.39 (s, 3 H, C(1)-CH_3), 6.90 ("d", $J \cong 5$ Hz, 2 H, C(4)-H + C(5)-H), 7.25 (m, 5 H, aromatic), 7.85 ("t", $J \cong 4$ Hz, 1 H, C(3)-H)

9j 6.73 (d, $J \cong 8.0$ Hz, 2 H, C(4)-H + C(5)-H), 6.93-7.46 (m, 11 H, aromatic), 7.75 (m, 4 H, aromatic ortho to C=O/C=N), 8.20 (dd, $J = 8.0$, 1.5 Hz, 1 H, C(3)-H)

9k 6.29-6.38 (m, 2 H, furan C(3)-H + C(4)-H), 6.63-6.75 (m, 2 H, C(4)-H + C(5)-H), 7.25-7.48 (m, 7 H, aromatic + furan C(5)-H), 7.72-7.98 (m, 4 H, aromatic ortho to C=O/C=N), 8.36 (dd, $J = 6.0$, 3.3 Hz, 1 H, C(3)-H)

9r 7.35-7.60 (m, 12 H, aromatic + C(5)-H), 7.75-8.07 (m, 4 H, aromatic ortho to C=O/C=N), 8.28 (s, 1 H, C(3)-H)

9s 1.44 (br m, 4 H, $-CH_2\mathbf{CH_2CH_2}CH_2-$), 1.95 (br m, 4 H, $-\mathbf{CH_2}CH_2CH_2\mathbf{CH_2}-$), 6.12 (m, 1 H, C(5)-H), 7.3 (m, 6 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N), 7.96 (s, 1 H, C(3)-H)

9t 1.66 (m, 4 H, $-\mathbf{CH_2}CH_2CH_2O-$), 4.26 (br t, $J \cong 5$ Hz, 2 H, $-CH_2CH_2\mathbf{CH_2}O-$), 6.79 (br s, 1 H, C(5)-H), 7.2 (m, 6 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N), 7.92 (s, 1 H, C(3)-H)

9u 2.16 (m, 2 H, $-\mathbf{CH_2}CH_2O-$), 3.06 (br t, $J \cong 6$ Hz, 2 H, $-CH_2\mathbf{CH_2}O$), 3.85 (br s, 2 H, $C{=}CCH_2O-$), 6.28 (m, 1 H, C(5)-H), 7.2 (m, 6 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N), 7.85 (s, 1 H, C(3)-H)

9v 1.66 (br q, $J \cong 7$ Hz, 2 H, $-CH_2\mathbf{CH_2}CH_2-$), 2.12 (m, 4 H, $-\mathbf{CH_2}CH_2\mathbf{CH_2}-$), 6.12 (m, 1 H, C(5)-H), 7.22 (m, 6 H, aromatic), 7.68 (m, 4 H, aromatic ortho to C=O/C=N), 8.22 (s, 1 H, C(3)-H)

9x 1.73 (m, 2 H, $-CH_2\mathbf{CH_2}CH_2-$), 2.67 (m, 4 H, $-\mathbf{CH_2}CH_2\mathbf{CH_2}-$), 6.87 (t, $J = 2.5$ Hz, 1 H, C(5)-H), 7.1 (m, 11 H, aromatic), 7.7 (m, 4 H, aromatic ortho to C=O/C=N)

11t 1.76 (m, 2 H, $-CH_2\mathbf{CH_2}CH_2O-$), 2.44 (br t, $J \cong 6$ Hz, 2 H, $-\mathbf{CH_2}CH_2CH_2O-$), 4.06 (br t, $J \cong 5$ Hz, 2 H, $-CH_2CH_2\mathbf{CH_2}O-$), 5.96 (br s, 1 H, -OH), 7.2 (m, 10 H, aromatic), 8.01 (s, 1 H, C(3)-H)

11x 1.96 (br, p,[b] $J \cong 7$ Hz, 2 H, $-CH_2\mathbf{CH_2}CH_2-$), 2.95 (br q, $J \cong 7$ Hz, 4 H, $-\mathbf{CH_2}CH_2\mathbf{CH_2}-$), 6.36 (s, 1 H, -OH), 6.9-7.8 (m, 15 H, aromatic)

12c 1.20 (t, $J = 6.0$ Hz, 3 H, $\mathbf{CH_3}CH_2O-$), 4.20 (q, $J = 6.0$ Hz, 2 H, $CH_3\mathbf{CH_2}O-$), 4.80 (s, 2 H, C(2)-H_2), 6.50 (s, 1 H, C(4)-H), 7.1-7.5 (m, 12 H, aromatic + vinyl)

12d 1.20 (t, $J = 6.0$ Hz, 3 H, $\mathbf{CH_3}CH_2O-$), 4.17 (q, $J = 6.0$ Hz, 2 H, $CH_3\mathbf{CH_2}O-$), 4.80 (s, 2 H, C(2)-H_2), 6.46 (s, 1 H, C(4)-H), 7.02-7.50 (m, 10 H, aromatic + vinyl)

12e 1.20 (t, $J = 6.7$ Hz, 3 H, $\mathbf{CH_3}CH_2O-$), 4.12 (q, $J = 6.7$ Hz, 2 H, $CH_3\mathbf{CH_2}O-$). 4.68 (s, 2 H, C(2)-H_2), 5.28 (d, $J_{PH} = 14.6$ Hz, 2 H, $-\mathbf{CH_2}P^+Ph_3Br^-$), 6.39 (d, $J_{PH} = 1.3$ Hz, 1 H, C(4)-H), 7.08-8.10 (m, 20 H, aromatic)

12f 1.20 (t, $J = 7.3$ Hz, 3 H, $\mathbf{CH_3}CH_2O-$), 4.16 (q, $J = 7.3$ Hz, 2 H, $CH_3\mathbf{CH_2}O-$), 4.70 (s, 2 H, C(2)-H_2), 5.34 (d, $J_{PH} = 14.0$ Hz, 2 H, $-\mathbf{CH_2}P^+Ph_3Br^-$), 6.39 (d, $J_{PH} = 1.3$ Hz, 1 H, C(4)-H), 7.1-8.2 (m, 19 H, aromatic)

12g 1.17 (t, $J = 7.0$ Hz, 3 H, $\mathbf{CH_3}CH_2O-$), 2.20 (s, 3 H, C(3)-CH_3), 4.10 (q, $J = 7.0$ Hz, 2 H, $CH_3\mathbf{CH_2}O-$), 4.63 (s, 2 H, C(2)-H_2), 6.00 (s, 1 H, C(4)-H), 7.3 (m, 4 H, aromatic)

12h 2.15 (s, 3 H, C(3)-CH_3), 6.02 (s, 1 H, C(4)-H), 6.50 (s, 1 H, C(2)-H), 7.1-7.3 (m, 12 H, aromatic), 7.5 (m, 2 H aromatic ortho to C=O)

12i 1.64 (d, $J = 7.0$ Hz, 3 H, C(2)-CH_3), 1.69 (s, 3 H, C(1)-CH_3), 4.77 (q, $J = 7.0$ Hz, 1 H, C(2)-H), 6.25 (d, $J = 1.5$ Hz, 1 H, C(4)-H), 7.31 (s, 5 H, aromatic), 7.46 (d, $J = 1.5$ Hz, 1 H, C(3)-H)

12j 6.16 (d, $J = 1.5$ Hz, 1 H, C(4)-H), 6.58 (s, 1 H, C(2)-H), 7.18 (br s, 13 H, aromatic), 7.4 (m, 3 H, C(3)-H + aromatic ortho to C=O)

12k 6.45-6.58 (m, 3 H, C(2)-H + furan C(3)-H, C(4)-H), 7.25 (s, 1 H, C(4)-H), 7.35-7.56 (m, 9 H, aromatic + furan C(5)-H), 7.78-7.93 (m, 3 H, aromatic ortho to C=O and C(3)-H)

12l 2.06 (s, 3 H, C(5)-CH_3), 5.93 (d, $J = 1.5$ Hz, 1 H, C(4)-H), 6.86 (s, 1 H, C(2)-H), 7.2 (m, 8 H, aromatic), 7.76 (d, $J = 1.5$ Hz, 1 H, C(3)-H), 7.6-8.0 (m, 2 H, aromatic ortho to C=O)

12m 1.89 (s, 3 H, C(4)-CH_3), 6.47 (s, 1 H, C(2)-H), 7.13 (br s, 13 H, aromatic), 7.24 (s, 1 H, C(3)-H), 7.5 (m, 2 H, aromatic ortho to C=O)

12n 2.09 (s, 3 H, C(3)-CH_3), 5.99 (s, 1 H, C(4)-H), 6.50 (s, 1 H, C(2)-H), 7.16 (br s, 13 H, aromatic), 7.45 (m, 2 H, aromatic ortho to C=O)

12o 2.22 (s, 3 H, C(3)-CH_3), 6.35 (s, 1 H, C(2)-H), 6.43 (d, $J = 1.3$ Hz, 2 H, furan C(3)-H, C(4)-H), 7.15 (s, 1 H, C(4)-H), 7.25-7.70 (m, 9 H, aromatic and furan C(5)-H), 7.75-7.93 (m, 2 H, aromatic ortho to C=O)

12p 6.63 (s, 1 H, C(4)-H[c]), 6.68 (s, 1 H, C(2)-H), 7.2-7.75 (m, 20 H, aromatic)

12q 6.94 (s, 1 H, C(4)-H[c]), 7.05-7.95 (m, 21 H, aromatic + C(2)-H)

12r 6.67 (s, 1 H, C(2)-H), 7.31-7.46 (m, 13 H, aromatic), 7.56-7.81 (m, aromatic ortho to C=O) + 7.59 (s, C(3)-H) - total 3 H

12s 1.6 (m, 4 H, $-CH_2\mathbf{CH_2}\mathbf{CH_2}CH_2-$), 2.3 (m, 4 H, $-\mathbf{CH_2}CH_2CH_2\mathbf{CH_2}-$), 6.78 (s, 1 H, C(2)-H), 7.15 (br s, 8 H, aromatic), 7.30 (s, 1 H, C(3)-H), 7.75 (m, 2 H, aromatic ortho to C=O)

12u 2.34 (m, 2 H, $-\mathbf{CH_2}CH_2OCH_2-$), 3.64 (br t, $J \cong 5.5$ Hz, 2 H, $-CH_2\mathbf{CH_2}OCH_2-$), 4.48 (br s, 2 H, $-CH_2CH_2O\mathbf{CH_2}-$), 6.95 (s, 1 H, C(2)-H), 7.11 (s, 8 H, aromatic), 7.27 (s, 1 H, C(3)-H), 7.76 (m, 2 H, aromatic ortho to C=O)

12v 2.36 (m, 6 H, $-CH_2CH_2CH_2-$), 7.02 (s, 1 H, C(2)-H), 7.08 (s, 1 H, C(3)-H), 7.16 (s, 8 H, aromatic), 7.8 (m, 2 H, aromatic ortho to C=O)

12w 1.67 (m, 4 H, $-CH_2\mathbf{CH_2}\mathbf{CH_2}CH_2-$), 2.5 (m, 4 H, $-\mathbf{CH_2}CH_2CH_2\mathbf{CH_2}-$), 6.54 (s, 1 H, C(2)-H), 7.2 (br s, 13 H, aromatic), 7.5 (m, 2 H, aromatic ortho to C=O)

12x 2.5 (m, 6 H, $-CH_2CH_2CH_2-$), 6.54 (s, 1 H, C(2)-H), 7.22 (br s, 13 H, aromatic), 7.5 (m, 2 H, aromatic ortho to C=O)

[a] Chemical shifts reported as parts per million δ vs. Me_4Si in $CDCl_3$ solution. [b] Numbering as in Table V; pentet. [c] Assignments for C(2)-H and C(4)-H may be reversed.

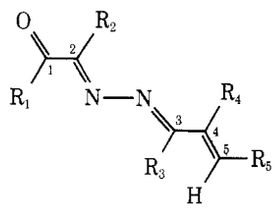
for 29 h. After concentration in vacuo to ~20 mL, precipitation into 500 mL of anhydrous ether yielded 3.7 g (90%) of **12f** as a colorless solid. Recrystallization from CH_2Cl_2-EtOAc afforded an analytical sample.

Hydrolysis of 17. Preparation of Triphenyl-2-carboethoxymethylidenehydrazonopropylidenephosphorane (18). A solution of 7.6 g (0.01 mol) of ylide salt **17** in 50 mL of methylene chloride was stirred for 8 h with 100 mL of 10% Na_2CO_3. After drying ($MgSO_4$) and removal of most of the solvent in vacuo, the methylene chloride layer was added dropwise to 300 mL of ethyl acetate. The orange solid which precipitated was shown (TLC, NMR) to be a mixture of ylide 18 and triphenylphosphine oxide. We were unable to completely separate 18 from Ph_3PO, and the mixture was used as is in further reactions: ^{1}H NMR δ 0.7-1.3 (br m, $\mathbf{CH_3}CH_2O$), 2.30 (s, $CH_3C{=}N$), 3.0-4.3 (br m, $CH_3\mathbf{CH_2}O$ + $\mathbf{CH}{=}PPh_3$), 7.05 (s, $-N{=}\mathbf{CH}-$), 7.15-7.0 (m, aromatic 18 + Ph_3PO).

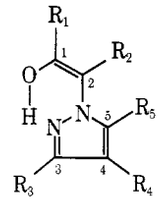
Preparation of Ethyl 1-[3-methyl-5-(4-chlorophenyl)pyrazolyl]acetate (12g). To 40 mL of benzyl alcohol was added the mixture of 18 and Ph_3PO prepared as above from 3.8 g (0.005 mol) of ylide salt 17 and 0.8 g (0.0057 mol) of 4-chlorobenzaldehyde. The solution was refluxed for 12 h, poured into water, and extracted with two 100-mL portions of ether. After drying ($MgSO_4$) and concentration in vacuo, the ether extracts afforded a thick oil, which was chromatographed [silica gel, pentane-ether (2:1) as eluent] to yield 1.0 g (74%) of **12g** as a pale yellow oil. Distillation at 220 °C (10 mm) yielded a colorless analytical sample which solidified on standing.

Preparation of Triphenyl-2-(phenylphenacylidenehydrazono)propylphosphium Bromide (23). A slurry of 9.2 g (0.041 mol) of benzil monohydrazone (**22**) and 15.2 g (0.04 mol) of porpargyltriphenylphosphonium bromide (14) in 40 mL of chloroform was heated at reflux for 2 h. The clear solution was then added dropwise to 600 mL of boiling benzene, stirred at ambient temperatures for 1 h, and filtered. The filter cake was recrystallized from methylene chloride-ethyl acetate to yield 19.6 g (83%) of **23** as a pale yellow solid: mp 224-225 °C; ^{1}H NMR δ 2.50 (d, $J_{PH} = 1.3$ Hz, 3 H, CH_3), 5.41 (d, $J_{PH} = 13.3$ Hz, 2 H, CH_2), 7.02-8.00 (m, 25 H, aromatic).

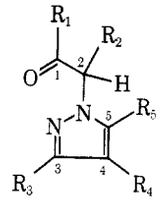
Table V. Selected ^{13}C NMR Parameters for Azines (9) and Pyrazoles (11/12) Prepared from α-Diketone Monohydrazones and α,β-Unsaturated Aldehydes and Ketones



9



11



12

Compd	C(1)	C(2)	C(3)	C(4)	C(5)	Other
9i	199.0[a]	161.7[b]	159.5	*d*	143.6	11.4; C(2)–CH_3 24.9; C(1)–CH_3
9j	197.3	166.4[b]	164.0	*d*	143.7	
9k	197.4	166.3[b]	163.5	*d*	144.1	112.2, 112.7; β-furyl 152.0; α-furyl
9r	197.2	167.4	160.9	119.2	140.9	
9s	197.6	166.5[b]	164.6	*d*	141.8	21.7, 22.1, 23.2, 26.4; $-(CH_2)_4-$
9t	198.1	164.5[b]	162.5	113.8	155.5	18.5, 21.0, 67.5; $-(CH_2)_3O-$
9u	197.0	167.2	160.7	*d*	137.4	26.1, 63.5, 64.0; $-CH_2O(CH_2)_2-$
9v	197.5	166.6	158.9	*d*	143.5	22.8, 30.3, 33.6; $-(CH_2)_3-$
9x	198.1	163.1	173.9	*d*	137.8	22.5, 29.6, 30.8; $-(CH_2)_3-$
11t	170.2	80.4	156.6[c]	113.2	166.8	20.9, 21.5, 68.1; $-(CH_2)_3O-$
11x	176.4	80.7	169.7[c]	*e*	158.4	22.8, 30.8, 34.3; $-(CH_2)_3-$
12i	204.0	62.6	139.9	106.6	144.6	16.2; C(2)–CH_3 26.0; C(1)–CH_3
12j	192.5	67.0	139.8	106.9	144.2	
12k	192.5	68.4	139.6	106.2	144.4	109.4, 111.6; β-furyl 142.7; α-furyl
12l	193.0	67.9	135.6	106.8	139.1	11.5; C(5)–CH_3
12m	193.1	67.3	140.5	115.4	141.3	9.0; C(4)–CH_3
12n	192.7	66.9	149.0	106.8	145.0	13.6; C(3)–CH_3
12p	192.5	67.4	151.4	104.1	145.6	
12o	192.5	68.0	148.7	106.0	144.4	13.5; C(3)–CH_3 109.2, 111.5; β-furyl 142.7; α-furyl
12q	193.0	69.1	*d*	111.3	*d*	197.8; C(5)–COPh
12r	192.4	68.3	140.5	94.9	141.7	
12s	193.2	68.1	135.6	117.2	137.4	20.7, 22.0, 22.8(2); $-(CH_2)_4-$
12u	193.3	68.7	135.2	115.8	136.4	23.5, 63.6, 68.6; $-(CH_2)_2OCH_2-$
12v	194.0	69.6	135.1	*e*	150.8	22.6, 25.0, 30.7; $-(CH_2)_3-$
12w	192.8	66.6	149.5	115.5	139.8	21.0, 23.2(2), 23.4; $-(CH_2)_4-$
12x	192.9	67.3	161.8	*e*	136.6	23.4, 25.0, 29.7; $-(CH_2)_3-$

[a] Parts per million δ vs. Me_4Si as internal standard in $CDCl_3$. [b] The assignments for C(2) and C(3) may be reversed. [c] The assignments for C(3) and C(5) may be reversed. [d] Unable to assign unambiguously. [e] Obscured by phenyl resonances.

Anal. Calcd for $C_{35}H_{30}BrN_2OP$: C, 69.43; H, 4.99. Found C, 69.26; H, 4.88.

Preparation of Triphenyl-2-(phenylphenacylidenehydrazono)propylidenephosphorane (24). In a 100-mL round-bottom flask was dissolved 2 g (~0.0358 mol) of potassium hydroxide in 40 mL of absolute ethanol. This solution was cooled to −15 °C (ice–methanol) and 9.7 g (0.0161 mol) of **23** was added with stirring. The deep red solution was then stirred at ambient temperatures for 30 min, during which an orange solid precipitates. Filtration and recrystallization from CH_2Cl_2–heptane afforded 8.0 g (93%) of **24** as yellow-orange crystals: mp 181–182 °C; ^1H NMR δ 2.42 (d, J_{PH} = 1.3 Hz, 3 H, CH_3), 2.98 (d, J_{PH} = 24.0 Hz, 1 H, $Ph_3P{=}CH$), 6.90–7.90 (m, 25 H, aromatic).

Anal. Calcd for $C_{35}H_{29}N_2OP$: C, 80.14; H, 5.55. Found: C, 79.81; H, 5.77.

Preparation of 3-Phenylphenacylidenehydrazono-1-(4-chlorophenyl)but-1-ene (9h). A solution of 2.0 g (3.8 mmol) of ylide **24** and 0.8 g (5.7 mmol) of 4-chlorobenzaldehyde in 20 mL of dry acetonitrile was heated at reflux for 2 h. Removal of solvent in vacuo afforded a yellow oil from which 0.7 g (52%) of **9h** was isolated by dry-column chromatography [Florisil (2 × 30 cm), 2.5:1 hexane–ether as eluent]. An analytical sample was prepared by crystallization from CH_2Cl_2–petroleum ether.

Preparation of 1-Phenyl-1-[3-methyl-5-(4-chlorophenyl)-pyrazolyl]acetophenone (12h). In a microstill was placed 1.0 g (3.75 mmol) of azine **9h**. Distillation at 260 °C (0.5 mm) yielded a pale yellow oil, which crystallized from methylene chloride–hexane to afford 0.5 g (50%) of pyrazole **12h** as a colorless solid.

Reactions of α-Diketone Monohydrazones (22 or 25) with α,β-Unsaturated Aldehydes and Ketones (26). General Method A. A solution of the hydrazone and carbonyl compound (5% excess) in absolute ethanol (50 mL/0.01 mol) was heated at reflux for the amount of time indicated in Table I. Small (10–15 mg) amounts of acetic or *p*-toluenesulfonic (*p*-TSA) acids were sometimes employed as catalysts and this is also noted in Table i. Cooling the reaction mixture or concentration/cooling initiated the crystallization of the listed products. Recrystallization from ethanol afforded analytically pure samples.

General Method B. A slurry of the hydrazone and carbonyl compound (5% excess) in benzene (50 mL/0.01 mol scale) was heated at reflux in a round-bottom flask fitted with a Dean–Stark water separater for the time indicated in Table I. After removal of the benzene in vacuo, crystallization of the residue from ethanol afforded the products listed in Table I.

Thermolysis of α-Oxo-α,β-unsaturated Azines. General Method. A sample (0.5–2.0 g) of the azine **9** was placed in a thick-walled glass tube, capped, and heated in an oil bath under the conditions listed in Table II. After cooling to room temperature, the crude product was dissolved in a minimal amount of CH_2Cl_2, diluted with ethanol (15 mL/g of azine), and treated with Darco G-60 activated carbon. The solution was filtered and the methylene chloride removed by gentle boiling for several minutes. Cooling led to the crystallization of the pyrazole products. The thermolysis of **9x** yielded a mixture of **11x** and **12x** which could only be separated by column chromatography (silica gel; CH_2Cl_2 as eluent).

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Registry No.—**9h,** 63569-86-8; **9i,** 63569-87-9; **9j,** 63569-88-0; **9k,** 63569-89-1; **9r,** 63569-90-4; **9s,** 63569-91-5; **9t,** 63569-92-6; **9u,** 63569-93-7; **9v,** 53569-94-8; **9x,** 63569-95-9; **11t,** 63569-96-0; **11x,** 63569-97-1; **12c,** 63569-98-2; **12d,** 63569-99-3; **12e,** 63570-00-3; **12f,** 63570-01-4; **12g,** 63570-02-5; **12h,** 63570-03-6; **12i,** 63570-04-7; **12j,** 63570-05-8; **12k,** 63570-06-9; **12l,** 63570-07-0; **12m,** 63570-08-1; **12n,** 63570-09-2; **12o,** 63570-10-5; **12p,** 63570-11-6; **12q,** 63570-12-7; **12r,** 63570-13-8; **12s,** 63570-14-9; **12u,** 63570-15-0; **12v,** 63570-16-1; **12w,** 63570-17-2; **12x,** 63570-18-3; **13,** 22610-15-7; **14,** 2091-46-5; **17** charged form, 63570-19-4; **17** uncharged form, 63570-20-7; **18** charged form, 63570-21-8; **18** charged form, 63570-22-9; **22,** 5344-88-7; **23,** 63570-23-0; **24** charged form, 63570-24-1; **24** unchanged form, 63570-25-2; **25,** 33487-48-8; **26a,** 104-55-2; **26b,** 623-30-3; **26c,** 4170-30-3; **26d,** 101-39-3; **26e,** 122-57-6; **26f,** 623-15-4; **26g,** 94-41-7; **26h,** 4070-75-1; **26i,** 5443-49-2; **26j,** 1192-88-7; **26k,** 25090-33-9; **26l,** 13417-49-7; **26m,** 6140-65-4; **26n,** 5682-83-7; **26o,** 5679-13-0; benzaldehyde, 100-52-7; 4-chlorobenzaldehyde, 104-88-1.

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Estimation of Allene Optical Purities by Nuclear Magnetic Resonance

W. H. Pirkle* and Charles W. Boeder

The Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

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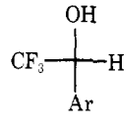
Methoxymercuration of chiral allenes affords chiral ethers, the enantiomeric purity and absolute configuration of which are related to those of the allenic precursor. Enantiomeric purity and absolute configuration of these allene derivatives can be determined by NMR using (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**1a**) as a chiral solvating agent. A solvation model is advanced to account for the origin and sense of the observed NMR nonequivalence of the enantiomeric derivatives in the presence of **1a**.

Despite considerable interest in the chemistry of chiral allenes, there is no general experimental method for the determination of enantiomeric purity of allenes lacking additional functionality. However, Brewster has calculated the rotational values expected for several chiral allenes including those without additional functional groups.[1] Chemical transformation of a chiral allene to a known chiral reference compound can provide enantiomeric purity data, although this approach is seldom used since most reactions that might be employed to modify the allenic functionality do not proceed stereospecifically. Thus far, the use of chiral solvating agents (CSA) as a direct method for determining enantiomeric purities of chiral allenes has been unsuccessful unless an additional "handle" is present.[2] An alternate indirect approach in which the chiral allene is stereospecifically converted to a chiral compound, the enantiomeric purity of which is then determined by NMR using a CSA, is the subject of the present paper.

Prior work with chiral type **1** fluoro alcohols has shown that these CSA render nonequivalent the NMR spectra of enantiomeric benzylic, allylic, or propargylic alcohols and their ethers. The oxymercuration of allenes in H_2O or methanol, believed to be a highly stereospecific reaction, affords mercury-containing allylic alcohols or methyl ethers. Owing to the sharp singlets arising from methoxyl groups, methoxymercuration is well suited to the overall process for NMR determination of enantiomeric purity. We have methoxymercurated several partially resolved simple allenes and used a type



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1 CSA to determine enantiomeric composition of the product ethers.

Methoxymercuration of allenes with mercuric acetate in methanol usually affords both cis and trans adducts and is considered to occur by the mechanistic pathway shown in Scheme I.[3] This scheme predicts that the two adducts will be of opposite chirality.[3]

Reaction of (*R*)-(−)-2,3-pentadiene (**2**), $[\alpha]^{25}_D$ −14.5° (1, Et_2O), with $Hg(OAc)_2$ in dry methanol at 25 °C followed by exchange of acetate for chloride affords a 6:1 ratio of trans:cis 3-chloromercuri-4-methoxy-2-pentenes, **3t** and **3c**, respectively. In CCl_4 solution with 3 equiv of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (**1a**) the mixture of **3t** and **3c** shows NMR nonequivalence of the enantiotopic methoxyl resonances for each isomer. Although the sense of nonequivalence and enantiomeric purity of **3c** in the mixture could not be reliably determined due to the proximity of other signals, the enantiomeric purity of (*S*)-**3t**, the major isomer, was ascertained to be 9.2%, with the methoxyl signal of the major enantiomer occurring at a higher field than that of the minor enantiomer (high field "sense" of nonequivalence). This value represents the *minimum* enantiomeric enrichment for **2**,