spectively. Preparative GC (Apiezon L) purification of the final (76%) component followed by ^{1}H NMR spectroscopy confirmed that this component was (*E*)-1-phenyl-1-butene. The second (12%) and fourth (4%) components were shown by GC coinjection *not* to be any of the other $C_{10}H_{12}$ isomers on hand and were presumed to be (*E*)- and (*Z*)-1-phenyl-2-butenes, respectively.

Isomerization of 2 at 70 °C. To 7.6 mL of 0.41 M potassium *tert*-butoxide in *tert*-butyl alcohol was added 250 mg of **2** in 1 mL of *tert*-butyl alcohol. The mixture was heated in an oil bath at 70 °C, and 1-mL samples were removed at 3, 9, and 72 h. The samples were worked up as described above and analyzed by analytical GC (XF-1150); three components were present with area ratios as follows: time (ratio in order of elution), 3 h (6:27:67), 9 h (7:8:85), 72 h (8:<0.1:92). GC coinjection showed the peaks to be, respectively, (*Z*)-1-(*o*-tolyl)propene, **2**, and (*E*)-1-(*o*-tolyl)propene. The first and third components were isolated by preparative GC (Apiezon L) and shown to be (*Z*)- and (*E*)-1-(*o*-tolyl)propenes, respectively, by ^{1}H NMR spectroscopy.

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Registry No. 1, 768-56-9; **2**, 1587-04-8; allyl chloride, 107-05-1; benzyl bromide, 100-39-0; *o*-tolyl bromide, 95-46-5; benzaldehyde, 100-52-7; *o*-tolualdehyde, 104-87-0; (*Z*)-1-(*o*-tolyl)propene, 2077-33-0; (*E*)-1-phenyl-2-butene, 935-00-2; (*Z*)-1-phenyl-1-butene, 1560-09-4; (*Z*)-1-phenyl-2-butene, 15324-90-0; (*E*)-1-(*o*-tolyl)propene, 2077-34-1; (*E*)-1-phenyl-1-butene, 1005-64-7.

Dehydrative Ring Closure of Some α-Pyrazolyl Ketones. Anomalous Closure of 1-Phenyl-1-[3-methyl-5-(2-naphthyl)pyrazolyl]-acetophenone to 2-Methyl-4,5-diphenylbenzo[*g*]pyrazolo[5,1-*a*]isoquinoline

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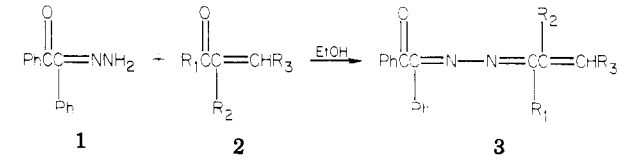
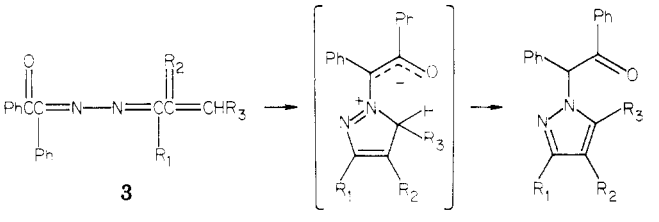
During the past years we have been studying the intermolecular cycloaddition reactions of acyclic azines.[2a] The products obtained in these reactions are sharply in contrast with the intra- and intermolecular cycloaddition reactions observed for all carbon,[3] monoaza,[4] and other diaza[5] dienes.

The desired azines **3** were readily prepared by allowing α-diketo monohydrazones **1** to react with the appropriate α,β-unsaturated carbonyl species **2**.[6] Cyclizations of the



1 2 3

azines produced, occurring at a variety of temperatures ranging from the reaction temperature of the formation of the azines **3** to 180 °C, gave N-substituted pyrazoles **4**.[6]



3 4

In this note the preparation of a series of pyrazolo[5,1-*a*]isoquinolines **5** (and **6**) by the dehydrative ring closure of the corresponding pyrazoles **4** (Table I) is reported. The X-ray analysis of the major, anomalous, ring-closure product from **4d** is discussed.

The normal ring closure of a large number of β-naphthyl derivatives by cyclodehydration have yielded compounds obtained by attack, mostly or exclusively, at the α position of the naphthyl moiety.[7] Therefore, we expected that the dehydrative ring closure of the pyrazole species **4d** with a β-naphthyl substituent in the 5 position (R_3) would yield the diaza steroidal backbone, **6a**, with nitrogens in the 13 and 17 positions. A number of diazasteroids[8] have been prepared although none with this particular orientation of the nitrogen atoms.

Treatment of the 1-phenyl-[3-methyl-5-(2-naphthyl)-pyrazolyl]acetophenone (**4d**) with polyphosphoric acid followed by quenching in water gave two products: one soluble in methylene chloride (81% yield) and one insoluble in methylene chloride (5% yield).

The structures of the two products were related, as shown by the ^{1}H NMR spectra (Table II); however, we could not determine if the ring closure to give the major product occurred in the normal manner to give **6a** or if it gave **6b**. Adequate quantities of the sample we list in Tables I and II as **6a** were not available in order to obtain a correct analyses, therefore the assignment of the steroidal backbone for this structure is only presumed. In order to determine the structure of the major product, the methylene chloride soluble fraction, it was submitted to an X-ray analysis. The X-ray crystallographic analysis[9] of the major product showed that its structure was **6b**, what we would designate as the abnormal[7] ring closure product.

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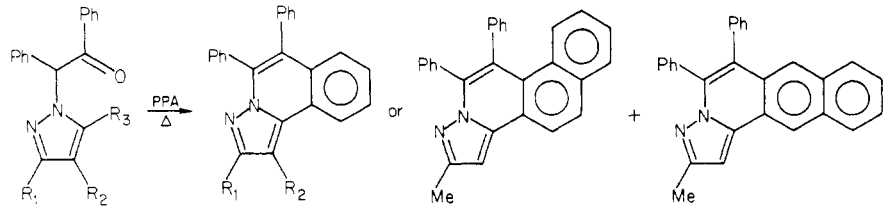
Table I. Preparation of Pyrazolo[5,1-*a*]isoquinolines 5 (or 6) by PPA Cyclodehydration of N-Substituted Pyrazoles 4



4 5 6a 6b

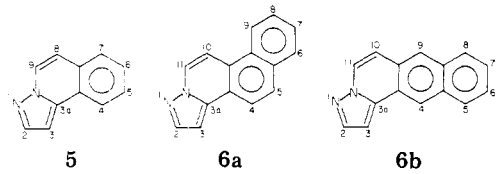
pyrazole	R_1	R_2	product	% yield	mp, °C	anal calcd for	anal found
4a	H[a]	H	5a	89	224-225	$C_{23}H_{16}N_2$, *m/e* 320.131	*m/e* 320.129
b	Me[a]	H	5b	96	236-237	$C_{24}H_{18}N_2$, *m/e* 334.147	*m/e* 334.147
c	H[a]	Me	5c	63	208-209	$C_{24}H_{18}N_2$: C, 86.19; H, 5.43	C, 86.48; H 5.53
d	Me[b]	H	6a	5	292-294 dec	no results	
			6b	81	244-246	X-ray	

[a] R_3 = Ph. [b] R_3 = β-Naphthyl.

Table II. ^{1}H NMR Parameters for the Pyrazolo[5,1-*a*]isoquinolines 5 and 6[a,b]

compd	chemical shift, δ
5a	7.10 (d, 1, *J* = 2.2 Hz, C(3)H), 7.17-7.58 (m, 14, aromatic), 7.97 (d, 1, *J* = 2.2 Hz, C(2)-H), 8.18 (d, 1, *J* = 7.7 Hz, C(7)H)
5b	2.62 (s, 3, CH_3), 6.89 (s, 1, C(3)H), 7.15-7.56 (m, 14, aromatic), 8.26 (d, 1 H, *J* = 7.9 Hz, C(7)-H)
5c	2.75 (s, 3, CH_3), 7.18-7.55 (m, 14 aromatic), 7.78 (s, 1, C(2)H), 8.32 (d, 1, *J* = 8.1 Hz, C(7)-H)
6a	2.7 (s, 3, CH_3), 7.3 (s, 1, C(3)H), 7.4-8.1 (m, 14, aromatic) 8.32 (d, 1, *J* = 8 Hz, C(4)H), 8.65 (d, 1, *J* = 9 Hz, C(9)H)
6b	2.52 (s, 3, CH_3), 7.22 (s, 1, C(3)H), 7.3-7.8 (m, 14, aromatic) 8.08 (s, 1, C(4)H), 8.85 (s, 1, C(9)H)

[a] Proton NMR spectra were recorded with a Bruker HFX-10/250 or a Perkin-Elmer R12-b instrument on ~10% $CDCl_3$ solutions. The exception was that of 6a which was recorded in trifluoroacetic anhydride solution. [b] The numbering systems used in 5, 6a, and 6b (for NMR purposes) are as follows:



5 6a 6b

Table III. Selected ^{13}C NMR Parameters for Pyrazolo[5,1-*a*]isoquinolines 5 and 6[a]

compd	C(2)	C(3)	C(3a)	C(9)	other
5a	140.9	97.6	133.1[b]	136.1	
5b	150.7	97.4	133.4[b]	136.6	14.4, C(2)-CH_3
5c	142.5	105.3	133.6[b]	136.7	12.0, C(3)-CH_3
6b	150.0	99.0	133.2[b]	136.4[c]	14.2, C(2)-CH_3

[a] Numbering as in Table II; NMR spectra recorded with a Brucker HFX-10/250 instrument. [b] The assignments for C(3a) and C(9)—or C(11) compound 6b—may be reversed. [c] C(11).

This product, 2-methyl-4,5-diphenylbenzo[*g*]pyrazolo-[5,1-*a*]isoquinoline (**6b**), crystallizes with two independent molecules in the unit cell. The two molecules of **6b** are similar except for the tilts of the external phenyl groups. In one form (A) the phenyl groups are approximately normal to the principal ring system while in the second form (B) they are tilted by approximately 20° from the normal. A second feature of the two conformational forms of molecule **6b** is that the benzopyrazoloisoquinoline moiety of neither molecule is planar and that the principal ring system of A is substantially more bowed than that of B.

A model of the desired reaction product, the azasteroid **6a**, was generated by computer graphics,[10,11] using the coordinates for A of **6b** as a starting point. Analysis of the geometry of this structure of **6a** indicates that the hydrogen (9-H in **6a** in Table II) and the phenyl carbon atoms would be separated by only 1.8 Å while the sum of their van der Waal's radii is 2.9 Å. This implies that severe buckling of the principal ring system is required for the formation of the normal[7] cyclodehydration product **6a** and this accounts for the difficulty with which it is formed.

Thus is has been shown that pyrazole derivatives **4** may be cyclized but that only minor amounts of the presumed diazasteroid **6a** are formed from **4d**. Work on the preparation of less sterically hindered 13,17-diazasteroidal systems is being explored.

Experimental Section

All of the α-pyrazolyl ketones, **4**, were prepared by the methods described in ref 6. Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected.

All of the compounds gave their calculated molecular weight as the major (100% of the base peak) peak in the mass spectral analysis except **5a** and **5c** which showed $M^+ - 1$ as 100% of the base peak. ^{13}C NMR parameters are given in Table III.

General Cyclodehydration Reaction of 4. The pyrazolyl ketone **4** (1 g) was heated for 3 h at 175 °C in 20 g of polyphosphoric acid. The resulting black mixture was added to 20 mL of water. After being stirred for 5 min the resulting yellow aqueous mixture was extracted with three 15-mL portions of methylene chloride. The combined organic layers were dried ($MgSO_4$, anhydrous) and concentrated to dryness. Two recrystallizations from ethanol (30/1 ethanol/product ratio) gave the products listed in Table I. The exception was **6a** which was obtained as a water and methylene chloride insoluble side product from the extraction of **6b** from water with methylene chloride.

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The Triisopropylsilyl Group as a Hydroxyl-Protecting Function

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A number of hindered triorganosilyl groups have been employed for the purpose of masking hydroxyl functions.[1-3,6] Among the more well-known of these are the *tert*-butyldimethylsilyl (TBDMS)[1] and *tert*-butyldiphenylsilyl (TBDPS)[2] moieties. A central concern in these cases is the stability of silyl ethers thus obtained toward hydrolysis under acidic or basic conditions, as unmasking is ultimately desireable but must not occur in an untimely fashion. Relative hydrolytic stabilities are also of interest in those instances were two or more sites may be protected by different silyl groups.

Some time ago, we reported an improved method for the synthesis of triisopropylsilyl chloride (TIPS-Cl) by which this reagent could be readily obtained in high purity from inexpensive materials.[4] From data then available on the rates of alkoxysilane hydrolysis,[5] it appeared that the TIPS group would represent a useful hydroxyl-protecting moiety which would be less easily removed than the TBDMS function. Indeed, independent work detailing stabilities of TIPS and other silyl-protected nucleosides and nucleotides soon appeared, based on a less convenient preparation of TIPS-Cl.[6] However, wider use of TIPS-Cl as a blocking reagent has not occurred.

Table I contains data on the relative ease of removal of TBDMS, TIPS, and TBDPS groups from a primary (1-butanol) and a secondary (cyclohexanol) alcoholic site. All silyl ethers were readily prepared from the appropriate silyl chloride and alcohol in dimethylformamide with imidazole catalysis.[1,7] A comparison of hydrolysis rates under acidic conditions indicates progressively less facile cleavage for both classes of silyl ethers along the series TBDMS, TIPS, TBDPS. In both primary and secondary cases, the rate difference between the TBDMS ether and the TIPS derivative is such so as to make only the TIPS group acceptable if acidic conditions needed for the purpose of other transformations must be maintained for more than a minute or so. This rate difference is in fact large enough to allow the selective removal of the TBDMS group in the presence of the TIPS group at or just below ambient temperatures in a relatively short time. Acid hydrolysis rate differences observed between TIPS and TBDPS derivatives of the alcohols examined indicate significantly faster cleavage of the TIPS ethers, particularly for the primary silyl ethers.

Table I. Half-Life of Silyl Ethers R_3SiOR' Under Desilylation Conditions[a]

	R′				
	n-butyl		cyclohexyl		
R_3	H^+	OH^-	H^+	OH^-	F^-
TBDM	<1 min	1 h	<4 min	26 h	76 min
TIP	18 min	14 h	100 min	44 h	137 min
TBDP	244 min	<4 h	360 min	14 h	*b*

[a] Acid hydrolysis: 1% HCl/95% EtOH/22.5 °C. Base hydrolysis: 5% NaOH/95% EtOH/90 °C. Fluoride ion cleavage: 2 equiv of *n*-Bu_4NF/THF/22.5 °C. [b] Not determined.

Base-induced desilylation of all ethers examined was much slower than respective acid-catalyzed hydrolysis, and even at 90 °C, half-lives on the order of hours were observed. An interesting reversal in hydrolysis rates vs. the acid-catalyzed results is noted in that the TBDPS derivatives are cleaved faster than the TIPS ethers. These TBDPS rates are, in fact, close to the TBDMS rates, an observation which is presaged by Sommer's report that under basic conditions menthoxytriphenylsilane is cleaved at approximately the same rate as the corresponding trimethylsilyl ether.[5]

The method of choice for unmasking silyl ethers under weakly basic conditions has employed tetra-*n*-butylammonium fluoride in tetrahydrofuran.[1] This reagent was found to effect the removal of cyclohexyl TIPS ether within a convenient time frame (e.g., overnight) at ambient temperatures and thus provides a useful alternative to the acid-catalyzed cleavage conditions.

In sum, several advantages can be envisioned for the use of the TIPS group as a hydroxyl-protecting moiety: (1) low cost and ready availability of pure TIPS-Cl, (2) greater stability of TIPS over TBDMS ethers, (3) more facile acidic deprotection of TIPS over TBDPS derivatives, and (4) relatively high volatility of TIPS ethers for purposes of gas chromatographic and mass spectral analysis.

Experimental Section

General. Infrared (IR) data were obtained on neat films, using a Beckman Acculab 4 spectrophotometer. ^1H NMR data was obtained on CCl_4 solutions containing tetramethylsilane or benzene (taken as δ 7.24), using a Varian A60-A spectrometer. Gas chromatographic (GC) analyses were performed on a Varian 1720 gas chromatograph with a thermal-conductivity detector, using a 5 ft × 0.25 in. 3% SE-30 stainless steel column. TBDMS-Cl and TBDPS-Cl were commercially obtained; the latter was significantly contaminated with diphenyldichlorosilane. Triisopropylsilyl chloride was prepared from triisopropylsilane as reported.[4] Triisopropylsilane was obtained by a modification of the procedure of Nametkin et al.[8] The Grignard reagent prepared from 8.0 mol of isopropyl chloride and 8.3 mol of magnesium turnings in 4 L of THF was treated at 0 °C with 2.0 mol of trichlorosilane and allowed to stir for 3 days at 25 °C. Workup and distillation through a 10-in. Vigreux column gave triisopropylsilane (80% based on $HSiCl_3$), bp 53–63 °C (18 mm), which was 95% pure by GC analysis.

Alkyl Silyl Ether Preparation. All alkyl silyl ethers were prepared by stirring a mixture of alcohol, chlorosilane, imidazole (1:1.2:2.5 molar ratio), and dimethylformamide (2 mL/g of alcohol)

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