Reactions of Azines. 11. Preparation of 4*H*-Pyrazolo[1,5-*c*][1,3,5]oxadiazines

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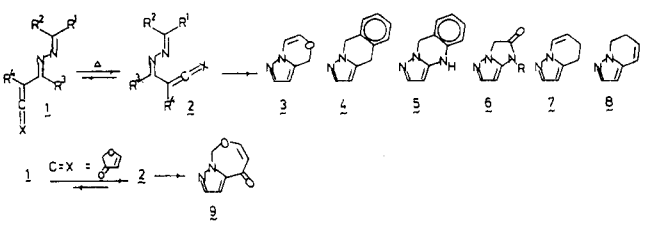
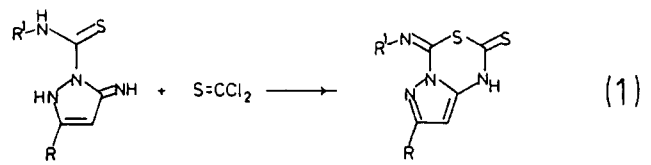
The title compounds were prepared by allowing acyl isocyanates to react with azine phosphoranes **14**. Phenylacetyl isocyanate lost HNCO on reacting with **14** and gave 2,3-dimethyl-4,6,7-triphenyl-4*H*-pyrazolo-[5,1-*c*][1,4]oxazine (**19**).

Over the past years we have shown that azines **1**, especially with cumulated moieties (such as allenes, ketene imines, or thioketenes), are useful synthons for the preparation of fused pyrazolo heterocycles. Up to the present time we have reported on the synthesis of the following ring systems in good to excellent yields: pyrazolo[5,1-*c*]-1,4-oxazines **3**,[1,2] 4,5-dihydropyrazolo[1,5-*b*]isoquinolines **4**,[1-3] 4,9-dihydropyrazolo[5,1-*b*]quinazolines **5**,[4] 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-2-ones **6**,[4,5] 4,5- and 6,7-dihydropyrazolo[1,5-*a*]pyridines (**7** and **8**),[6] and 4*H*,8*H*-pyrazolo[1,5-*c*][1,3]oxazepin-4-ones **9**.[7]



A literature search uncovered a synthesis of 4*H*-pyrazolo[1,5-*c*][1,3,5]thiadiazines **12** (eq 1);[8] however, no report was found for the preparation of 4*H*-pyrazolo[1,5-*c*][1,3,5]oxadiazines **16**.

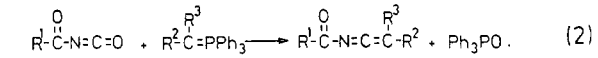


(1)

10 **11** **12**

In this paper we wish to reveal an extension of the usefulness of azines as synthons for the preparation of fused pyrazolo species by synthesizing compounds of structure **16**.

Earlier we disclosed[4,5] that when phosphoranes **14**, prepared from the corresponding phosphonium salts **13**,[9] were allowed to react with alkyl or aromatic isocyanates, only pyrazolo[5,1-*b*]quinazolines **5** and/or imidazo[1,2-*b*]-pyrazol-2-ones **6** were produced apart from the triphenylphosphine oxide normally found in a Wittig olefination reaction. In addition, it has been shown[10] that when ylides, with no protons on the carbon α to the phosphorus moiety, react with acyl isocyanates, the expected ketene imines were formed (eq 2). The ylides **14** were allowed



(2)

to react with acyl isocyanates, and the formation of the azine ketene imines **1a–f** is presumed[4,10] (Scheme I).

The corresponding 4*H*-pyrazolo[1,5-*c*][1,3,5]oxadiazines **16** were formed by ring closure via the zwitterionic species **15**. However, the oxadiazines **16** may have been formed directly via a [4 + 2] intramolecular cycloaddition from **2**.

The isolation of a dimer from a zwitterionic reaction intermediate from a comparable reaction[5] and reactions to give compounds of structure **6**[4,5] would suggest that pathway **14** → **1** → **2** → **15** → **16** (Scheme I) provides a reasonable mechanism for the formation of **16**. The possibility of more than one competing pathway for the ring-closure reactions of cumulated azine species of type **1** is not ruled out and is being explored in a system where the intermediate **1** is stable and isolable.

The reaction of phenylacetyl isocyanate did not give the expected **16f**. The pyrazolo product obtained was the known 2,3-dimethyl-4,6,7-triphenyl-4*H*-pyrazolo[5,1-*c*]-[1,4]oxazine (**19**) (Scheme II). None of the reactions of acyl isocyanates with phosphoranes reported in the literature[10] gave anything but ketene imines and triphenylphospine oxide. It is difficult to envision a feasible mechanism for the formation of **19** from **1**, **2**, or **15**. We therefore conclude that the initial step in the formation of **19** from **14** and phenylacetyl isocyanate is the loss of cyanic acid giving phenylketene **17**. This reaction is essentially identical with the reaction reported[2] for phenylacetyl chloride with triethylamine except that in this case the ylide **14** would be the base instead of triethylamine. Reaction of **14** with **17** would then give **19** via the intermediate **18**.[2]

The preparation of other novel fused pyrazolo heterocycles from azines will be reported in the future.

Mass Spectrometric Analyses. None of the compounds **16a–d**, containing the benzoyl moiety (R^2 = PhCO) on the carbon α to the bridgehead nitrogen, gave a correct exact mass. All of these species gave mass 105 (PhCO) as the major peak and M^+ – PhCO as the major peak con-

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Scheme I

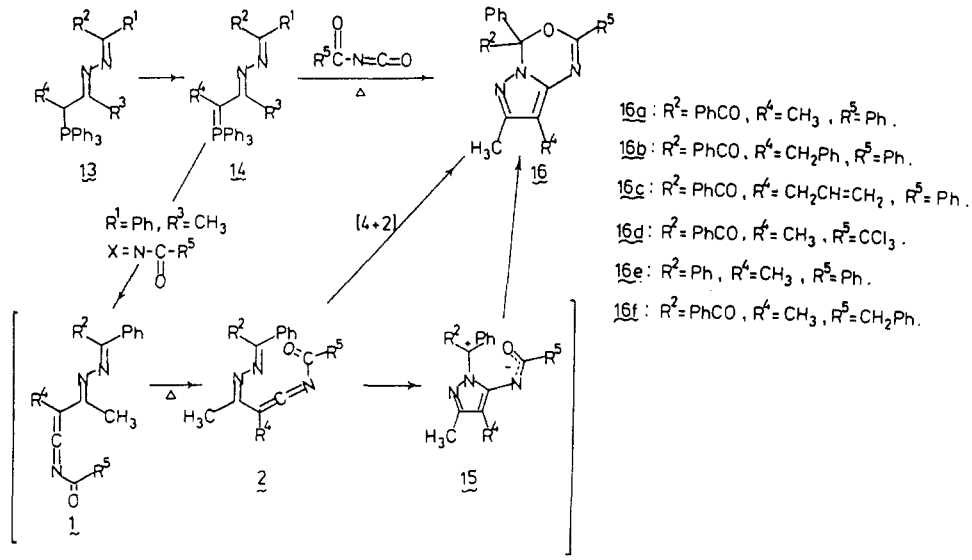
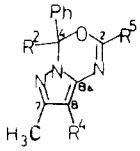


Table I. Preparation of 4*H*-Pyrazolo[1,5-*c*][1,3,5]oxadiazines 16[a] from Ylide 14[b] and Isocyanate ($R^5CON{=}C{=}O$)

							^1H NMR ($CDCl_3$) δ		
compd	R^2	R^4	R^5	yield, %	mp, °C	formula[c]	C_7-CH_3	Ar	others
16a	PhCO	CH_3	Ph	52	144–145[d]	$C_{26}H_{21}N_3O_2$	2.20 (s, 3 H)	7.24–8.04 (m, 15 H)	2.12 (s, 3 H, C8-CH_3)
16b	PhCO	$PhCH_2$	Ph	51	122–123[e]	$C_{32}H_{25}N_3O_2$	2.10 (s, 3 H)	7.16–8.04 (m, 20 H)	3.91 (d, J = 15.7 Hz, 1 H, CH_2Ph), 4.01 (d, J = 15.7 Hz, 1 H, CH_2Ph)
16c	PhCO	$CH_2{=}CHCH_2$	Ph	55	157–158[e]	$C_{28}H_{23}N_3O_2$	2.19 (s, 3 H)	7.24–8.03 (m, 15 H)	3.35 (m, 2 H, CH_2), 5.06 (m, 2 H, $=CH_2$), 5.98 (m, 1 H, CH=)
16d	PhCO	CH_3	CCl_3	42	142–143[f]	$C_{21}H_{16}Cl_3N_3O_2$	2.19 (s, 3 H)	7.26–7.83 (m, 10 H)	2.11 (s, 3 H, C8-CH_3)
16e	Ph	CH_3	Ph	58	196–197[f]	$C_{25}H_{21}N_3O$	2.22 (s, 3 H)	7.24–7.40 (m, 13 H), 8.12–8.16 (m, 2 H)	2.12 (s, 3 H, C8-CH_3)

[a] Numbering of 16 shown in Table II. [b] In ylide 14, R^1 = Ph, R^3 = CH_3. [c] The microanalyses were in satisfactory agreement with the calculated values (±0.2% for C, H). [d] Recrystallized from hexane. [e] Recrystallized from hexane–ether. [f] Recrystallized from ether.

Table II. Selected ^{13}C NMR Spectral Data for 4*H*-Pyrazolo[1,5-*c*][1,3,5]oxadiazines 16



				^{13}C NMR, ppm							
compd	R^2	R^4	R^5	C2[a]	C4	C7	C8	C8a	C7-CH_3	PhCO	misc
16a	PhCO	CH_3	Ph	153.4	94.5	150.1	109.1	139.1	12.7	191.4	7.0 (C8-CH_3)
16b	PhCO	$PhCH_2$	Ph	153.9	94.6	150.2	112.3	140.5	12.9	191.3	28.3 (CH_2Ph), 26.6 ($CH_2CH{=}CH_2$)
16c	PhCO	$CH_2{=}CHCH_2$	Ph	153.7	94.5	150.2	110.9	139.3	12.8	191.3	115.0 ($CH_2CH{=}CH_2$), 136.3 ($CH_2CH{=}CH_2$)
16d	PhCO	CH_3	CCl_3	150.8	95.9	150.1	112.4	137.1	12.6	190.1	7.0 (C8-CH_3), 90.6 (CCl_3)
16e	Ph	CH_3	Ph	154.4	95.4	149.2	108.5	139.3	12.6		6.9 (C8-CH_3)

[a] Assignment based on ref 11.

taining the pyrazolo[1,5-*c*][1,3,5]oxadiazine fragment.

Only from **16e** was the correct exact mass obtained for the structure proposed.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt capillary apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra of approximately 10% (w/v) solutions in $CDCl_3$ were obtained on a Bruker Spectrospin Model WM 250. Chemical shifts were reported in parts per million (δ scale) vs. tetramethylsilane as an internal standard.

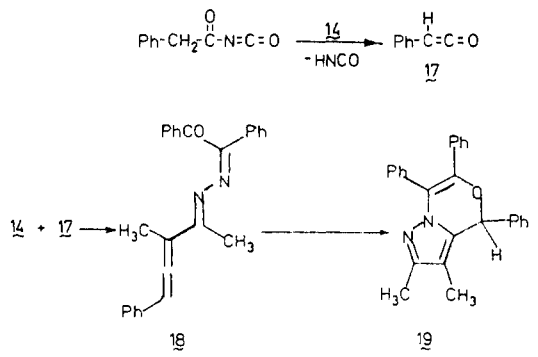
Dry nitrogen gas was routinely employed as the reaction atmosphere in all reactions. Toluene was dried and distilled from sodium metal. All glassware was baked at 130 °C for a minimum of 4 h before use. Baker silica gel (60–200 mesh) and EM 7747 silica gel for column chromatography were used throughout for product separation.

Precise mass spectra were recorded by using a Du Pont 21-492B instrument with a resolution of 3300. Elemental analyses were performed by Micro Analysis, Inc., Wilmington, DE.

The phosphoranes **14** were produced by known methods.[9] The isocyanates employed were prepared according to Speziale and Smith.[12]

(12) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1963**, *28*, 1805; **1965**, *30*, 4306.

Scheme II



Preparation of 4*H*-Pyrazolo[1,5-*c*][1,3,5]oxadiazines 16. General Method. A solution of the phosphorane 14 (2.0 mmol) and acyl isocyanate (2.5 mmol) in 20 mL toluene was stirred at room temperature for 30 min and then under reflux for 2 h. The solvent was removed in vacuo, and the residue was chromatographed on a silica gel column by eluting with ethyl acetate/hexane (1/7), yielding first the 4*H*-pyrazolo[1,5-*c*][1,3,5]oxadiazine **16** and then triphenylphosphine oxide. Recrystallization of **16** from ether and/or hexane (as indicated in Table I) afforded a colorless analytically pure sample. Isolated yields, melting points, ^{1}H NMR (Table I), and ^{13}C NMR (Table II) were collected separately.

Reaction of Phosphorane 14 with Phenylacetyl Isocyanate. The reaction was undertaken in the manner described above in General Method. The chromatographed product was recrystallized from an ether/hexane mixture to yield the known 2,3-dimethyl-4,6,7-triphenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazine **19** (46%). The melting point, mixed melting point, and ^{1}H and ^{13}C NMR were identical with those of the previously reported sample.[2]

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Reaction of 2-Aryl-3-(*N*,*N*-dimethylamino)-1-propenes and Their Corresponding Quaternary Ammonium Salts with Organometallic Species and Reducing Agents

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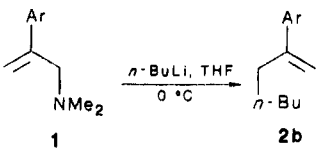
A series of 2-aryl-3-(*N*,*N*-dimethylamino)-1-propenes and their corresponding quaternary ammonium salts were reacted with a variety of organometallic species and reducing agents. The utility of such reactions for the preparation of α-substituted styrene derivatives is discussed.

We have recently reported[1] that a variety of 2-aryl-3-(*N*,*N*-dimethylamino)-1-propenes react with butyllithium and *tert*-butyllithium in THF at 0 °C to produce the corresponding 3-substituted 2-aryl-1-propenes in good yield (Scheme I).

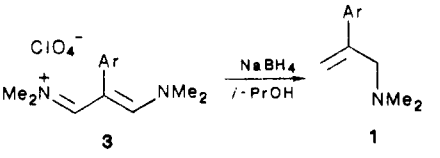
We believe this work to be interesting and useful in light of the recent studies by Richey[2] on the reaction of 1-aryl-3-(*N*,*N*-dimethylamino)-1-propenes with organolithium reagents. For example, Richey has reported that 1-(*N*,*N*-dimethylamino)-2-benzylhexane is produced as the major reaction product by the treatment of *n*-butyllithium with 1-phenyl-3-(*N*,*N*-dimethylamino)-1-propene in refluxing hexane. It has been suggested that the allylic amine group facilitates the addition of the organometallic reagent to the double bond by coordination with lithium.

Goering[3] and co-workers have also recently reported on the cross-coupling reactions of analogous allylic carboxylates with Grignard reagents under the influence of various Cu(I) salts. One example that was particularly intriguing to us was the regioselective addition of *n*-butylmagnesium bromide to the pivalate ester of 3-deuterio-2-phenyl-2-propenol to give 3-deuterio-2-phenyl-1-heptene in good yield.

Scheme I



Scheme II



Our interest in 2-aryl-3-(*N*,*N*-dimethylamino)-1-propenes stems from the fact that these substances are readily available[4] from the corresponding vinamidinium salts by sodium borohydride reduction (Scheme II).

Such systems are intriguing since the double bond has the potential of being activated to some extent by the aromatic ring. Magid[5] has extensively reviewed the nu-

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