thienyl.

Registry No. **2** (n = 2), 87350-64-9; **2** (n = 3), 87337-90-4; **3** (n = 2), 5660-45-7; **3** (n = 3), 86100-63-2; **4** (p = 2), 4743-21-9; **6** (p = 1, q = 0), 87337-91-5; **7** (n = 2), 5632-29-1; poly(2,5-thiophenediyl) (SRU), 51325-05-4; 1,1-dibromo-2-(2,2′:5′,2″-terthienyl-5-yl)ethylene, 87350-66-1; 2,2′:5′,2″-terthiophene-5-carboxaldehyde, 7342-41-8; 5-ethynyl-2,2′:5′,2″-terthiophene, 87337-92-6; bromo(2-thienyl)acetylene, 33675-51-3; 1-lithio-2-ethynylthiophene, 62439-93-4.

Formation of α-Cyanoaziridines and 1-(Alkylamino)cyclopropanecarbonitriles by Cyanation of α-Halo Ketimines[1]

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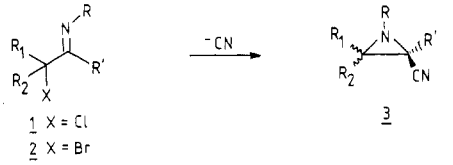
A new convenient synthesis of α-cyanoaziridines was developed by reaction of α-halo ketimines with cyanide in methanol or acetonitrile. Tertiary α-chloro ketimines with cyanide in methanol gave rise to a competitive reaction between α-cyanoaziridine formation and production of 1-(alkylamino)cyclopropanecarbonitriles, the latter being classified as a Favorskii rearrangement-type product. The scope and limitations of this reaction have been determined by investigation of reaction parameters such as the nitrogen substituent, the solvent, the inorganic cyanide, the carbon skeleton, and the nature of the α-halogen.

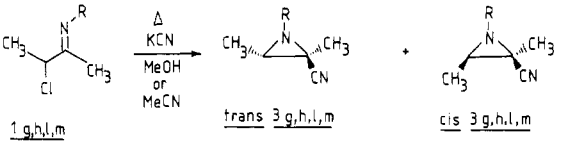
In a preliminary communication, we described a novel synthesis of α-cyanoaziridines **3** by reaction of α-chloro ketimines **1** with potassium cyanide in methanol (Scheme I).[3] Such α-cyanoaziridines are an important class of organic compounds, and much attention has been devoted to them because they are able to undergo 1,3-cycloadditions to, for example, olefins or alkynes via azomethine ylides.[4-6]

These functionalized aziridines have been previously prepared by various methodologies, including reaction of primary amines with α-halogeno-α,β-unsaturated nitriles[7-10] or condensation of α,β-unsaturated nitriles with nitrenes,[11] N-unsubstituted oxaziridines,[12] and organic azides.[13] Alternative methods of preparation involved substitution by cyanide of α-chloroaziridines,[14] reaction of α-chloro nitriles with aromatic aldimines in alkaline medium (i.e., the analogue of the Darzen reaction),[15] addition of diazoacetonitrile to certain aldimines,[16] or reaction of Δ^1-pyrroline N-oxides with the anion derived from diethyl cyanomethylphosphonate.[17] The principle interest

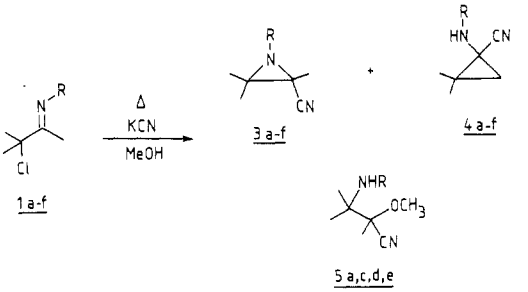
Scheme I



Scheme II



Scheme III



(1) This is part 31 of our series dealing with the chemistry of α-halogenated imines. For part 30, see: De Kimpe, N.; Sulmon, P.; Verhé, R.; De Buyck, N.; Schamp, N. *Tetrahedron Lett.* **1983**, *24*, 2885.
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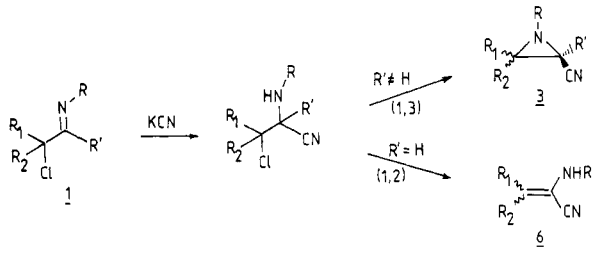
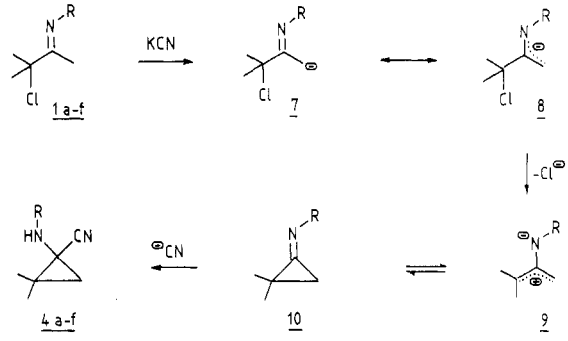
Scheme IV



Scheme V



in this class of compounds originates from the potential to furnish the above-mentioned 1,3-dipolar cycloaddition, but more recently it has been found that α-cyanoaziridines possess cancerostatic and immunostimulating properties.[3,18,19] In view of these chemical and medicinal properties, the scope and limitations of the new synthesis of α-cyanoaziridines **3** from α-halo ketimines **1** and **2** were investigated.

Results and Discussion

Reaction of secondary *N*-alkyl α-chloro ketimines **1g,h,i,l,m** (R_2 = H; R = *i*-Pr, methyl, cyclohexyl, allyl, *t*-Bu) with 1.5–2 equiv of potassium cyanide in methanol under reflux (1–2 h) afforded a mixture of cis and trans α-cyanoaziridines **3** in high yield (Scheme II; Table I, entries 7–11). Both stereoisomers were easily separated by preparative gas chromatographic analysis. The same reaction in acetonitrile was much slower and required an overnight reflux period. This is a remarkable result because tertiary α-chloro ketimines **1a–e** ($R_2 \neq$ H; R = *i*-Pr, cyclohexyl; Et, allyl, *neo*-Pe) showed a faster reaction with potassium cyanide in acetonitrile to afford α-cyanoaziridines **3** as the sole products. If the reaction of these tertiary α-chloro ketimines was performed with potassium cyanide in methanol, then a competitive reaction between α-cyanoaziridine formation (**3**) and cyclopropanation to yield compounds **4** was noticed (Scheme III; Table I, entries 1–6). α-Cyanoaziridines **3a–f** were always the major compounds and were accompanied by 12–22% of functionalized cyclopropanes **4a–f**. In a few cases, small amounts (2–9%) of ring-opened compounds **5** were isolated by preparative gas chromatography. Because α-cyanoaziridines **3**, on reaction with cyanide in methanol, did not afford nitriles **5**, the formation of the latter may originate from opening by cyanide of an intermediate α-methoxyaziridine. Table I gives a survey of the reaction of α-halo ketimines **1** and **2** with cyanide under various conditions. The spectrometric properties (NMR, IR, mass spectra) of α-halo ketimines **1** and **2**, and α-cyanoaziridines **3** are compiled in Tables I and II of the supplementary material section.

The formation of α-cyanoaziridines **3** is explained by nucleophilic addition of cyanide at the imino function of α-chloro ketimines to yield an adduct (or its anion), which subsequently undergoes intramolecular nucleophilic substitution. This reaction pathway did not permit the synthesis of α-cyanoaziridines **3** (R′ = H) having an α-hydrogen because the cyanide adduct of α-chloroaldimines **1** (R′ = H) furnished α-cyanoenamines **6** by 1,2-dehydrochlorination due to the fact that this reaction is initiated by deprotonation of the acidic hydrogen, α with respect to the nitrile moiety (Scheme IV).[20] Cyclopropane derivatives **4** originate from trapping by cyanide of cyclopropylideneamines **10**, which are formed by formal base-induced 1,3-dehydrochlorination of α-chloro ketimines **1a–f**. Therefore, this reaction can be classified as a part of the Favorskii rearrangement. The Favorskii rearrangement is well-known in organic chemistry as the base-induced skeletal rearrangement of α-halo ketones to afford carboxylic acid derivatives via cyclopropanone intermediates (the semibenzilic type rearrangement is less frequently encountered).[21] During the last decade, successful efforts have been undertaken to induce also a Favorskii rearrangement with α-halogenated imines,[22–25] i.e., the corresponding nitrogen analogues of α-halogenated ketones. The intermediates in this reaction, i.e., cyclopropylideneamines (= cyclopropanone imines), have been isolated under similar circumstances,[25,26] and some evidence has been presented for the exclusion of the semibenzilic-type mechanism.[22] The results of the trapping of cyclopropylideneamines **10** by cyanide, reported in this communication, might be an additional proof that the mechanism of the Favorskii rearrangement of α-halo ketimines passes through intermediate cyclopropylideneamines (e.g., **10**). This Favorskii-type reaction is initiated by α′-deprotonation of α-chloro ketimines **1a–f** to generate delocalized anion **8**, which looses spontaneously a chloride anion. The resulting zwitterionic species **9** is in equilibrium with cyclopropylideneamine **10** via disrotative ring-closure (ring-opening) according to the rules of Woodward and Hoffmann. The strained heteromethylenecyclopropane **10** is subsequently trapped by cyanide to furnish stable adducts, i.e., 1-(alkylamino)-2,2-dimethylcyclopropanecarbonitrile (**4**) (Scheme V). These adducts are stable, easy-to-handle derivatives of the difficultly accessible cyclopropylideneamines (e.g., **10**), which are members of the important class of heteromethylenecyclopropanes.[27] Previously, only very few 1-aminocyclopropanecarbonitriles were synthesized, namely, by S_N1 reaction of cyanide with 1-(dialkylamino)cyclopropanols (or their silyl ether) or aminals derived from cyclopropanone.[28–30] It should be

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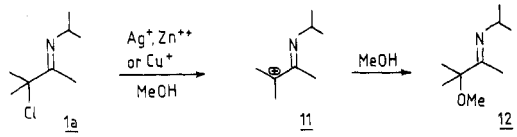
Table I. Reactions of α-Halo Ketimines 1 and 2 with Cyanide under Various Conditions

entry	starting material	R	R′	R_1	R_2	reaction conditions[a]	α-cyano-aziridine 3,[b] %	cyclo-propane-carbo-nitrile 4, %	remarks[c]
1	**1a**	*i*-Pr	Me	Me	Me	2E KCN/MeOH; Δ 1.5	86 (73)	12	bp **3a**: 69–73 °C (18 mmHg) 2% nitrile **5a**
2	**1b**	cyclohexyl	Me	Me	Me	2E KCN/MeOH; Δ 2	86 (70)	12	bp **3b**: 119–122 °C (14 mmHg)
3	**1c**	Et	Me	Me	Me	2E KCN/MeOH; Δ 3	75	16	9% nitrile **5c**
4	**1d**	allyl	Me	Me	Me	2E KCN/MeOH; Δ 3	77	15	8% nitrile **5d**
5	**1e**	*neo*-Pe	Me	Me	Me	2E KCN/MeOH; Δ 20	73	22	5% nitrile **5e**
6	**1f**	$PhCH_2$	Me	Me	Me	2E KCN/MeOH; Δ 20	88	12	compound **3f** could not be purified by preparative GLC
7	**1g**	cyclohexyl	Me	Me	H	1.5E KCN/MeOH; Δ 1.5	95 (73)	0	cis/trans 1:2 bp **3g**: 123–130 °C (18 mmHg)
8	**1h**	allyl	Me	Me	H	2E KCN/MeOH; Δ 23	60	0	15% *N*-allyl-3,3-dimethoxy-2-butylamine (ref 45) *cis*-**3h**/*trans*-**3h** 1:1
9	**1i**	Me	Me	Me	H	2E KCN/MeOH-Et_2O (2:1); Δ 5	(26)	0	bp 130–135 °C (760 mmHg)
10	**1l**	*t*-Bu	Me	Me	H	1.5E KCN/MeOH; Δ 1.5	96 (74)	0	trans isomer **3l**, exclusively bp **3l**: 70–75 °C (11 mmHg)
11	**1m**	*i*-Pr	Me	Me	H	2E KCN/MeOH; Δ 10	76 (88)	0	cis/trans 1:2 bp **3m**: 58–66 °C (13 mmHg)
12	**1a**	*i*-Pr	Me	Me	Me	2E KCN/EtOH; Δ 7	87	13	
13	**1a**	*i*-Pr	Me	Me	Me	2E KCN/Me_2SO, 60 °C/18 h	100	0	
14	**1a**	*i*-Pr	Me	Me	Me	2E KCN/DMF; 60 °C/14 h	100	0	
15	**1a**	*i*-Pr	Me	Me	Me	2E KCN/CH_3CN; Δ 20	100 (86)	0	bp see entry 1
16	**1l**	*i*-Pr	Me	Me	H	2E KCN/CH_3CN; Δ 20	100	0	cis/trans 18:82
17	**1m**	*i*-Pr	Me	Me	H	2E KCN/CH_3CN; Δ 24	80	0	recovery of 20% **1m**
18	**1a**	*i*-Pr	Me	Me	Me	2E NaCN/MeOH; Δ 3	90 (82)	10	bp see entry 1
19	**1a**	*i*-Pr	Me	Me	Me	2E $Zn(CN)_2$/MeOH; Δ 20	59	2	38% 3-methoxy-3-methyl-2-butanone RM: 70% yield
20	**1a**	*i*-Pr	Me	Me	Me	2E CuCN/MeOH; Δ 20	3	0	RM: 45% yield, mainly 3-methoxy-3-methyl-2-butanone
21	**1a**	*i*-Pr	Me	Me	Me	2E AgCN/MeOH; Δ 4	74	0	26% α-methoxy ketimine **12**
22	**2a**	*i*-Pr	Me	Me	Me	2E KCN/MeOH; Δ 19	100	0	
23	**2j**	*i*-Pr	Et	Me	Me	2E KCN/MeOH; Δ 4	100	0	
24	**2k**	*i*-Pr	*i*-Pr	Me	Me	2E KCN/MeOH; Δ 1.5	94 (89)	0	~5% (2,4-dimethyl-1-penten-3-ylidene)isopropylamine bp **3k**: 78–82 °C (12 mmHg)
25	**1o**	*i*-Pr	Me	Ph	H	2E KCN/MeOH; Δ 1.5	90 (82)	0	isolated by column chromatography (silica gel; CCl_4: ether, 8:2)
26	**1o**	*i*-Pr	Me	Ph	H	2E KCN/CH_3CN; Δ 20	95	0	cis/trans (80–90:20–10)
27	**1p**	*i*-Pr	Me	Ph	Me	2E KCN/MeOH; Δ 48	17	0	complex reaction mixture; *cis*-**3p** isolated by preparative column chromatography (mp 205 °C)
28	**1g**	cyclohexyl	Me	Ph	H	2E KCN/MeCN; Δ 16	86 (59)	0	100% cis (mp 106 °C)

[a] E = equivalents; Δ = reflux in hours. [b] Yields in parentheses refer to isolated yields (distillation); other yields refer to GLC analyses; reaction mixtures were isolated in nearly quantitative yield, except when otherwise stated. [c] RM = reaction mixture.

Scheme VI



pointed out that carbinol amines or aminals of cyclopropanones have been found previously to be the precursors of choice for cyclopropanones, cyclopropylideneamines, and cyclopropanimmonium derivatives,[31] which have been shown to be versatile synthons for natural products[30,32] and heterocyclic compounds, including β-lactams[31,33-35] and 1-pyrrolizidinones.[30] Because of the fact that geminally substituted cyclopropanes, such as compounds 4, seem to have a great potential in synthetic organic chemistry and because their hydrolyzed derivatives are homologues of 1-aminocyclopropanecarboxylic acid, the well-known precursor for the phytohormone ethylene,[36,37] attempts were made to alter the competition between formation of α-cyanoaziridines 3 and 1-(alkylamino)-cyclopropanecarbonitriles 4 on reaction of α-halo ketimines **1a–f** with cyanide ion. Influencing factors such as the nitrogen substituent, the solvent, the inorganic cyanide, the nature of the α-halogen, and the carbon skeleton have been studied in detail (more detailed information concerning this parameter study will be the subject of a separate publication).

Changing the *nitrogen substituent* (R = *i*-Pr, Et, cyclohexyl, allyl, benzyl; Table I, entries 1–6) did not drastically effect the ratio between α-cyanoaziridines 3 (75–88%) and 1-(alkylamino)cyclopropanecarbonitriles 4 (12–16%). Only the more sterically hindered *N*-neopentyl derivative **1e** with potassium cyanide in methanol yielded 22% cyclopropanederivative **4e**, the remainder being α-cyanoaziridine **3e** (73%).

Methanol and ethanol are the preferential *solvents* (Table I, entries 1–6, 12) for the formation of cyclopropylideneamine adducts 4 from *N*-alkyl α-chloro α-methyl ketimines **1a–f**. These reactions proceed with a nearly quantitative yield, α-cyanoaziridines being the major end products (78–89%). A quantitative conversion of *N*-isopropyl α-chloro ketimine **1a** with potassium cyanide into α-cyanoaziridine **3a** was noticed in acetonitrile, dimethyl sulfoxide, or dimethylformamide, but the addition of crown ethers, e.g., 15-crown-6, did not change the result. No trace of cyclopropane derivative **4a** could be identified with these reactions in nonalcoholic medium (Table I, entries 13–17). The nature of the *cyanide* (Table I, entries 1, 18–21) played an important role. The reaction of *N*-isopropyl α-chloro ketimine **1a** with potassium and sodium cyanide in methanol at reflux afforded comparable results (**3a**/**4a** 88–90%/12–10%), while zinc cyanide, copper(I) cyanide, or silver cyanide in methanol gave rise to more complex reaction mixtures in which little or no cyclopropane derivative **4a** was found (Scheme VI). Instead, in the latter three cases, substantial amounts of 3-methoxy-3-methyl-2-butanone were isolated, originating from hydrolysis of the corresponding *N*-isopropyl α-methoxy ketimine **12**, resulting itself from methanolysis of the starting α-chloro ketimine **1a**. It is reasonable to assume that such metal cations induce a spontaneous solvent-assisted ionization of the halide **1a** to generate an α-imidoylcarbenium ion **11**, which is trapped by methanol to furnish the α-methoxy ketimine **12**. α-Imidoylcarbenium ions[38] are the nitrogen analogues of α-acylcarbenium ions, which have long been ignored in organic chemistry but whose chemistry has been fairly well developed during the last decade.[39]

Changing the *α-halogen* from chlorine to bromine did not result in any improvement of the formation of cyclopropanes **4**. As compared to tertiary α-chloro ketimines **1**, tertiary α-bromo ketimines **2a,j,k** ($R_1 = R_2$ = Me; X = Br; R = *i*-Pr; R′ = Me, Et, *i*-Pr) reacted with potassium cyanide in methanol under reflux to afford α-cyanoaziridines **3a,j,k** exclusively (besides 5% 1,2-dehydrobromination for **2k**) (Table I, entries 22–24). It seems that the α-bromo atom is more readily displaced by intramolecular nucleophilic substitution (cf. Scheme IV) than by a Favorskii-like process (cf. Scheme V). Because this Favorskii rearrangement is initiated by an α′-deprotonation, the introduction of alkyl groups at the α′-position renders these α′-protons less acidic and entirely disfavors this reaction as compared to the α-cyanoaziridine formation.

The influence of the *carbon skeleton* is further investigated by reactions of α-phenylated α-chloro ketimines (Table I, entries 25–28). α-Phenyl α-chloro ketimines **1o–q** (R = *i*-Pr, cyclohexyl; R_1 = Ph; R_2 = H, Me) afforded mainly cis α-cyanoaziridines **3o,p** by reaction with potassium cyanide in acetonitrile or methanol (the trans isomer was present in 0–20%). The abscence of cyclopropanecarbonitrile (analogeous to **4**) originates from preferred aziridine formation because of the doubly activated halide moiety (heteroallylic and benzylic) in compounds **1o–q**. By gas chromatographic analysis these cis isomers **3o,p** are completely transformed into the corresponding trans derivatives **3o,p**. However, a quantitative conversion from cis α-cyanoaziridine **3o** to trans α-cyanoaziridine **3o** was not obtained because partial fragmentation into benzylideneisopropylamine (**17a**) appeared to be a competitive reaction. This fragmentation reaction is not very clear but presumably results from decomposition of an intermediate azomethine ylide (e.g., **13**). The possible carbene or carbenoid fragment (e.g., 1-cyano-1-methylcarbene) or following products could not be identified. The transformation of cis α-cyanoaziridines **3o,p** into trans α-cyanoaziridines **3o,p** proceeds by conrotatory opening of the C–C bond followed by isomerization of the intermediate azomethine ylide **13** into **14** and subsequent ring-closure. Such azomethine ylides (e.g., **13**) can be trapped by primary amines to afford a functionalized aminal which decomposes to give the corresponding benzylideneamine **17** (Scheme VII). As an example, cis α-cyanoaziridine **3o** was reacted with *tert*-butylamine in toluene under reflux to yield a 1:1:2 mixture of benzylidene-*tert*-butylamine (**17b**), benzylideneisopropylamine, and trans α-cyanoaziridine **3o**, respectively. These products resulted from azomethine ylide **13** (and/or **14**) by amine addition (**13** → **17b**), breakdown to **17a**; and isomerism to the trans isomer **3o**, respectively (Scheme VII). A similar amine-induced fragmentation was

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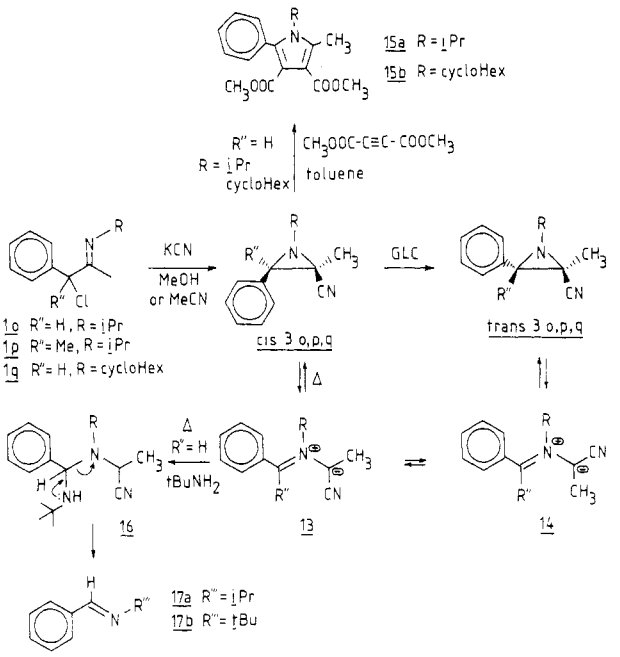
Scheme VII



observed with aziridines substituted with electron-withdrawing groups.[6] The thermal transformation of **3o** into aldimine **17a** parallels completely the photochemical cleavage of α-cyanooxiranes into a carbonyl fragment and a cyanocarbene moiety.[40]

The conversion of α-cyano-α′-phenylaziridines **3o–q** into azomethine ylides **13** and **14** has found application in the synthesis of heterocyclic compounds by 1,3-dipolar cycloaddition of azomethine ylides with olefins and alkynes.[4-6] As an example, *cis*-2-cyano-1-isopropyl-2-methyl-3-phenylaziridine (**3o**) and *cis*-2-cyano-1-cyclohexyl-2-methyl-3-phenylaziridine (**3q**) were transformed into dimethyl 1-isopropyl-2-methyl-5-phenylpyrrole-3,4-dicarboxylate (**15a**) and the corresponding *N*-cyclohexyl derivative **15b**, respectively (30–53% yield), by reaction with dimethyl acetylenedicarboxylate in toluene. On the contrary, aliphatic α-cyanoaziridines **3** did not give this 1,3-dipolar cycloaddition, in accordance with findings that the introduction of an aromatic substituent in α-cyanoaziridines has a great activating effect on the rate of opening into azomethine ylides.[4,6]

Secondary α-chloro ketimines **1** (R_2 = H) with potassium cyanide in methanol could not be converted into 1-(alkylamino)cyclopropanecarbonitriles as α-cyanoaziridines **3** were the exclusive reaction products.

In conclusion to this parameter study, the best results for the generation of 1-(alkylamino)cyclopropanecarbonitriles **4** were obtained with tertiary *N*-alkyl α-chlorinated methyl ketimines **1a–f** and potassium cyanide in methanol, but the yields were very poor (max 22%) because the major, if not the exclusive, reaction led to α-cyanoaziridines.

All 1-(alkylamino)cyclopropanecarbonitriles **4** reported in this paper are new compounds and are fully characterized by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR, MS) (Tables III and IV of the supplementary material section). Geminally difunctionalized cyclopropanes **4** were characterized in their IR spectra by the sharp nitrile and N–H absorption at about 2220 and 3320 cm^{-1}, respectively. The ^{1}H NMR spectrum showed the typical AB system for the ring-methylene function (δ 0.7–1, J_{AB} ~ 5 Hz), together with the two singlets for the geminal dimethyls. In addition, ^{13}C NMR data completely support the proposed structure. Most typically, the resonances (δ, $CDCl_3$) for the carbons of the cyclopropane ring are situated at δ 37–38 (1-position), 26 (2-position), and 29 (3-position). On the other hand, the molecular ion in the mass spectrum was in accordance with the proposed structure of compounds **4**.

The spectrometric data of 23 α-cyanoaziridines **3** are compiled in Table II of the supplementary material section (IR, ^{1}H NMR, mass spectral data). The stereochemistry of α-cyanoaziridines **3** bearing only one substituent (usually methyl) at the 3-position was determined by ^{1}H NMR spectrometry and, in addition, by IR spectrometry. It was observed that the methyl at the 3-position resonated at much lower field for cis α-cyanoaziridines (δ 1.31–1.38) than for trans α-cyanoaziridines (δ 1.15–1.21). In addition, cis and trans α-cyanoaziridines **3** (R_1 or R_2 = H) were distinguished by the nitrile absorption, which was found to be 6–9 cm^{-1} lower for trans derivatives than for cis derivatives (Table II, supplementary material).

Finally it has to be underlined that the reaction of α-halo ketimines **1** and **2** with cyanide opens a new and facile way for the generation of α-cyanoaziridines **3**, which is analogous to the synthesis of the corresponding oxygen analogues (i.e., α-cyano epoxides) from α-halo ketones.[41-43]

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer Model 1310 spectrophotometer. ^{1}H NMR spectra were measured with a Varian T-60 NMR spectrometer (60 MHz), while ^{13}C NMR spectra were obtained with a Varian FT-80 NMR spectrometer (20 MHz). Mass spectra were recorded with a Varian Mat 112 mass spectrometer (direct inlet system) or a A.E.I. MS 20 mass spectrometer (coupled with a Pye Unicam gas chromatograph Model 104 using an on-column injection).

Synthesis of α-Halogenated Ketimines 1 and 2. α-Chloro ketimines **1** and α-bromo ketimines **2** were synthesized according to our previously published method involving condensation of α-halo ketones with primary amines in ether (or benzene) in the presence of titanium(IV) chloride.[44] In most cases, titanium(IV) chloride in pentane was added to a cooled ethereal solution of the α-halo ketone and the primary amine. When the α-halo ketone had reacted already with the primary amine in ether (as evidenced by a test-tube experiment), the inverse method was used, involving treatment of a preformed mixtures of α-halo ketone and titanium(IV) chloride in ether with the appropriate amine (dissolved in ether). Most reactions were run over 1 or 2 h at ambient temperature (the mixing of the reagents was performed at ice-bath temperature). Sterically hindered α-halo ketimines (e.g., (2-bromo-2,4-dimethyl-3-pentylidene)isopropylamine, **2k**) required a larger reaction time (30-h reflux in benzene). Regular sampling of the reaction is advisable in order to determine the degree of conversion (1 N NaOH/ether; test tube; GLC analysis or preferably NMR monitoring). Workup of all reaction mixtures was done with aqueous sodium hydroxide solution as described previously,[44] except in the case of less volatile amines (e.g., benzylamine) where the filtration method was used. Physical and spectral data of all new α-chloro and α-bromo ketimines **1** and **2** are compiled in Table I of the supplementary material section (compounds **1c–f**, **1h**, **1i**, **1n**, **1q**, **2a**, **2j**, **2k**). The remaining α-halo ketimines have been described in a previous paper.[44] All α-halo ketimines used in this paper gave halogen analyses in agreement

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with the proposed structures. All compounds described in this paper are obtainable in a purity of at least 98%, but in most cases no impurities greater than 1% are detected (GLC, spectrometric methods).

General Procedure for the Synthesis of α-Cyanoaziridines 3. A solution of 0.1 mol of α-halo ketimine 1 (or 2) in dry methanol (10% solution w/v) was treated with 0.15–0.20 mol of potassium cyanide. The heterogeneous mixture was stirred (magnetic bar) under reflux for the time indicated in Table I, cooled, and poured into water (~200 mL). Extraction was performed with ether or dichloromethane (three extractions), and the combined extracts were dried ($MgSO_4$) and evaporated to leave a clear oil, which was analyzed by gas chromatography and distilled. Physical and spectrometric data of α-cyanoaziridines **3** and 1-(alkylamino)-cyclopropanecarbonitriles **4** are brought together in Tables II–IV of the supplementary material section.

The results are given in Table I. In all cases, except where otherwise stated, reaction mixtures (usually colorless oils) were isolated in nearly quantitative yield (>97%). Distribution of products was verified by preparative gas chromatography and spectrometric methods (NMR). Separation of cis and trans α-cyanoaziridines was easily achieved by preparative GLC. All compounds could be obtained in very pure state (>98%) by preparative GLC. Elemental analyses of some representative compounds are given below. Table I gives the distribution of products along with isolated yields (by vacuum distillation) of α-cyanoaziridines **3**. Less volatile α-cyanoaziridines (e.g. **3o,p**) were isolated by column chromatography (silica gel, using 8:2 CCl_4:ether as eluents). A typical representative preparation of an α-cyanoaziridine is the following experiment. According to the above-mentioned procedure and according to entry 11, 14.75 g (0.1 mol) of (3-chloro-2-butylidene)isopropylamine (**1m**) was dissolved in 145 mL of methanol and treated with 13 g (0.2 mol) of potassium cyanide. After 10 h of reflux and the usual workup procedure (see above), there was obtained 13.4 g (97%) of a colorless reaction mixture, which by GLC and ^1H NMR analyses showed only the presence of cis and trans α-cyanoaziridines **3m**. The reaction mixture was distilled in vacuo to give a mixture (12.1 g; 88%) of pure cis and trans α-cyanoaziridines **3m**, bp 58–66 °C (13 mmHg).

***trans*-3m**: ^1H NMR (CCl_4) δ 1.12 and 1.15 (2 × 3 H, 2 × d, J = 6 Hz, $NC(CH_3)_2$) 1.15 (3 H, d, J = 5.5 Hz, CH_3CH), 1.35 (3 H, s, $CH_3CC{\equiv}N$), 1.85 (1 H, q, J = 5.5 Hz, MeC*H*), 2.15 (1 H, septet, J = 6 Hz, NCH); IR (NaCl) 2233 cm^{-1} ($\nu_{C\equiv N}$); mass spectrum, m/e (relative abundance) 138 (M^+, 7), 123 (2), 97 (17), 96 (35), 83 (3), 82 (5), 81 (1), 71 (5), 70 (11), 69 (100), 68 (47), 56 (5), 55 (7), 54 (10), 53 (7), 52 (5), 51 (2), 44 (5), 43 (30), 42 (49), 41 (27), 40 (5), 39 (12). Anal. Calcd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.41; H, 10.29; N, 20.42.

***cis*-3m**: ^1H NMR (CCl_4) δ 1.21 and 1.13 (6 H, d, J = 6 Hz, $NC(CH_3)_2$), 1.35 (3 H, d, J = 5.5 Hz, CH_3CH), 1.47 (3 H, s, $CH_3CC{\equiv}N$), 1.6–2.7 (2 × 1 H, broad, MeC*H* and NC*H*); IR (NaCl) 2242 cm^{-1} ($\nu_{C\equiv N}$); mass spectrum m/e (relative abundance) 138 (M^+, 9), 123 (1), 97 (15), 96 (33), 83 (3), 82 (6), 81 (3), 71 (4), 70 (12), 69 (100), 68 (46), 56 (5), 55 (7), 54 (11), 53 (8), 52 (5), 51 (2), 44 (8), 43 (33), 42 (49), 41 (29), 40 (6), 39 (12). Anal. Found: C, 69.48; H, 10.32; N, 20.44.

Another typical representative preparation involves the conversion of (3-chloro-3-methyl-2-butylidene)isopropylamine (**1a**) into 1-isopropyl-2,3,3-trimethylaziridine-2-carbonitrile (**3a**) and 1-(isopropylamino)-2,2-dimethylcyclopropanecarbonitrile (**4a**). From 161.5 g (1 mol) of α-chloro ketimine **1a**, 130 g (2 mol) of potassium cyanide, and 1.5 L of methanol there was obtained (according to the general procedure; entry 1, Table I) 147 g of a light-yellow oil. Distillation in vacuo over a Vigreux column afforded 111 g (73%) of pure α-cyanoaziridine **3a**, bp 69–73 °C (18 mmHg), and 21 g of a fraction, bp 74–84 °C (16 mmHg), which by GLC was shown to be a mixture of α-cyanoaziridine **3a** (42%), cyclopropanecarbonitrile **4a** (50%), and nitrile **5a** (8%). Pure samples of 1-(isopropylamino)-2,2-dimethylcyclopropanecarbonitrile (**4a**) and 3-(isopropylamino)-2-methoxy-2,3-dimethylbutyronitrile (**5a**) were obtained by preparative gas chromatography.

1-Isopropyl-2,3,3-trimethylaziridine-2-carbonitrile (3a): ^1H NMR (CCl_4) 1.05 and 1.13 (2 × 3 H, 2 × d, J = 6 Hz, $NC(CH_3)_2$), 1.15 (3 H, s, CH_3 trans with respect to C≡N), 1.37 (6 H, s broad, CH_3 cis with respect to C≡N and $CH_3CC{\equiv}N$), 2.55 (1 H, septet, J = 6 Hz, NCH); IR (NaCl) 2230 cm^{-1} ($\nu_{C\equiv N}$); mass spectrum, m/e (relative abundance) 152 (M^+, 4), 137 (0.5), 109 (58), 98 (2), 96 (2), 95 (5), 85 (5), 84 (8), 83 (21), 82 (44), 70 (3), 69 (3), 68 (7), 67 (3), 66 (2), 58 (3), 57 (2), 56 (2), 55 (3), 54 (3), 53 (5), 52 (3), 51 (2), 44 (6), 43 (12), 42 (100), 41 (20). Anal. Calcd for $C_9H_{16}N_2$: C, 71.01; H, 10.59; N, 18.40. Found: C, 70.86; H, 10.49; N, 18.56.

1-(Isopropylamino)-2,2-dimethylcyclopropanecarbonitrile (4a): ^1H NMR δ (CCl_4) 0.74 (1 H, d, AB part, J = 4.8 Hz, ring CH) (the other part of the AB system is covered, even invisible at 360 MHz, but it can be made visible by recording the spectrum in benzene: δ 0.33 and δ 0.68 (AB, J = 4.8 Hz)), 1.09 and 1.13 (2 × 3 H, 2 × d, J = 6 Hz, Me_2CN), 1.23 (3 H, s, CH_3 trans), 1.32 (3 H, s, CH_3 cis), 1.60 (1 H, br s, NH), 3.26 (1 H, septet, J = 6 Hz, NCH); IR (NaCl) 3305 cm^{-1} (ν_{NH}), 2222 ($\nu_{C\equiv N}$); mass spectrum, m/e (relative abundance) 152 (M^+, 7), 137 (4), 109 (36), 95 (100), 82 (31), 70 (20), 69 (16), 68 (68), 67 (7), 58 (6), 37 (8), 56 (25), 55 (20), 54 (10), 53 (11), 44 (22), 43 (93), 42 (37), 41 (73), 40 (25), 39 (31); ^{13}C NMR ($CDCl_3$) δ 120.81 (s, C≡N), 37.04 (s, NCC≡N), 29.19 (t, CH_2 ring), 25.90 (s, CMe_2), 23.46 (q, *Me*C(2) (cis)), 19.42 (q, *Me*C(2)(trans)), 22.86 and 23.02 (br, Me_2CN), 47.64 (d, CHN). Anal. Calcd for $C_9H_{16}N_2$: C, 71.01; H, 10.59; N, 18.40. Found: C, 70.92; H, 10.72; N, 18.53.

Satisfactory analyses (C, H, N) were also reported for **3b**, **3c**, **3l**, **3o**, and **4b**.

Besides α-cyanoaziridines **3** and 1-(alkylamino)cyclopropanecarbonitriles **4**, several other reaction products have been identified in one or another reaction described in Table I. Their spectra data, not included in the above-mentioned tables, are given below.

3-(Isopropylamino)-2-methoxy-2,3-dimethylbutyronitrile (5a, R = isopropyl): ^1H NMR (CCl_4) δ 0.9 (1 H, s, br, NH), 1.04 (6 H, d, J = 6 Hz, $NCMe_2$), 1.16 (6 H, s, Me_2), 1.46 (3 H, s, CH_3), 3.43 (3 H, s, OMe), 2.99 (1 H, septet, J = 6 Hz, NCH); IR (NaCl) 3360 cm^{-1} (ν_{NH}) 2235 ($\nu_{C\equiv N}$).

3-(Ethylamino)-2-methoxy-2,3-dimethylbutyronitrile (5c, R = Et): ^1H NMR ($CDCl_3$) δ 1.05 (3 H, t, J = 7 Hz, $NCCH_3$), 1.17 (6 H, s, br, Me_2), 1.51 (3 H, s, CH_3CCN), 2.62 (2 H, q, J = 7 Hz, NCH_2), 3.43 (3 H, s, OCH_3), 1.5 (1 H, s, NH); IR (NaCl) 3400 cm^{-1} (ν_{NH}); mass spectrum, m/e (relative abundance) 170 (no M^+), 155 (1), 139 (1.5), 128 (2), 123 (1), 86 (100), 70 (33), 58 (32), 44 (13), 43 (19), 42 (66), 41 (19), 40 (10).

3-(Allylamino)-2-methoxy-2,3-dimethylbutyronitrile (5d, R = allyl): ^1H NMR ($CDCl_3$) δ 1.20 and 1.22 (6 H, 2 × s, Me_2CN), 1.4 (1 H, s, br, NH), 1.53 (3 H, s, CH_3CCN), 3.45 (3 H, s, OCH_3), 3.25 (2 H, d + allylic coupling, J = 5.5 Hz), 4.9–6.2 (3 H, vinylic system, $CH{=}CH_2$); IR (NaCl) 3400 cm^{-1} (ν_{NH}), 2260 ($\nu_{C\equiv N}$), 1648 ($\nu_{C=C}$); mass spectrum, m/e (relative abundance) no M^+, 157 (3), 140 (3), 99 (9), 98 (100, $CH_2{=}CHCH_2{}^+NH{=}CMe_2$), 82 (14), 70 (13), 58 (11), 56 (11), 54 (9), 43 (20), 42 (31), 41 (100), 40 (14), 39 (20).

3-(Neopentylamino)-2-methoxy-2,3-dimethylbutyronitrile (5e, R = neopentyl): ^1H NMR ($CDCl_3$) δ 0.88 (9 H, s, *t*-Bu), 1.15 (6 H, s, Me_2), 1.53 (3 H, s, Me), 2.32 (2 H, s, NCH_2), 3.46 (3 H, s, OMe), NH invisible; IR (NaCl) 2260 cm^{-1} ($\nu_{C\equiv N}$); mass spectrum, m/e (relative abundance) no M^+, 197 (8), 181 (2), 180 (4), 165 (8), 155 (13), 128 (100, *t*-$BuCH_2{}^+NH{=}CMe_2$), 123 (40), 119 (8), 109 (6), 98 (9), 91 (6), 58 (8).

(3-Methoxy-3-methyl-2-butylidene)isopropylamine (12): ^1H NMR ($CDCl_3$) δ 1.10 (6 H, d, J = 6.5 Hz, Me_2CN), 1.83 (3 H, s, $CH_3C{=}N$), 1.27 (6 H, s, Me_2), 3.10 (3 H, s, OCH_3), 3.65 (1 H, s, septet, J = 6.5 Hz, NCH); IR (NaCl) 1660 cm^{-1} ($\nu_{C\equiv N}$).

(2,4-Dimethyl-1-penten-3-ylidene)isopropylamine: ^1H NMR ($CDCl_3$) δ 1.05 (6 H, d, J = 6.2 Hz, Me_2CN), 1.08 (6 H, d, J = 7 Hz, $Me_2CC{=}N$), 1.80 (3 H, m, $CH_3C{=}C$), 2.52 (1 H, septet, J = 7 Hz, $CHC{=}N$), 3.63 (1 H, septet, J = 6.2 Hz, NCH), 4.60 and 5.05 (2 H, 2 × m, $C{=}CH_2$); IR (NaCl) 1654 cm^{-1} ($\nu_{C\equiv N}$), 1635 ($\nu_{C=C}$); mass spectrum m/e (relative abundance) 153 (M^+, 5), 138 (3), 110 (18), 70 (13), 68 (100, $CH_2{=}C(Me)C{\equiv}{}^+NH$), 55 (7), 44 (3), 43 (20), 42 (5), 41 (25), 40 (12), 39 (7).

Conversion of α-Cyanoaziridines 3o,q into Functionalized Pyrroles 15. A solution of 0.01 mol of α-cyanoaziridine **3o** or **3q** in 20 mL of dry toluene, containing 0.011 mol of dimethyl acetylenedicarboxylate, was refluxed for 16 h. Evaporation of the solvent in vacuo afforded an oil from which crystalline **15a** (R = *i*-Pr) was isolated (standing overnight in refrigerator) or from

which the oily **15b** (R = cyclohexyl) was isolated by preparative thick-layer chromatography (silica gel; eluent ether–pentane 1:1).

Dimethyl 1-isopropyl-2-methyl-5-phenylpyrrole-3,4-dicarboxylate (15a): ^{1}H NMR ($CDCl_3$) δ 1.36 (6 H, d, J = 7 Hz, Me_2), 2.59 (3 H, s, CH_3), 3.57 (3 H, s, $COOCH_3$), 3.80 (3 H, s, $COOCH_3$), 4.34 (1 H, septet, J = 7 Hz, NCH), 7.36 (5 H, s, Ph); IR (KBr) 1724 and 1700 cm^{-1} ($\nu_{C=O}$); mass spectrum, m/e (relative abundance) 315 (M^+, 12), 283 (18), 282 (30), 242 (12), 241 (18), 181 (12), 58 (48), 43 (100), 40 (36); mp 116 °C. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.57; H, 6.65; N, 4.65.

Dimethyl 1-cyclohexyl-2-methyl-5-phenylpyrrole-3,4-dicarboxylate (15b): ^{1}H NMR (CCl_4) δ 0.9–2.2 (10 H, m, C_6H_{10}), 2.63 (3 H, s, CH_3), 3.53 (3 H, s, $COOCH_3$), 3.79 (3 H, s, $COOCH_3$), 3.8 (1 H, m, NCH), 7.2–7.5 (5 H, m, Ph); IR (NaCl) 1720–1690 cm^{-1} ($\nu_{C=O}$).

Reaction of *cis*-2-Cyano-1-isopropyl-2-methyl-3-phenylaziridine (3o) with *tert*-Butylamine in Toluene. A solution of 0.01 mol of α-cyanoaziridine **3o** and 0.05 mol of *tert*-butylamine in 20 mL of toluene was refluxed for 16 h, after which toluene and excess amine were evaporated in vacuo. The remaining oil was analyzed by preparative gas chromatography, which revealed the presence of benzylideneisopropylamine (**17a**), benzylidene-*tert*-butylamine (**17b**), and trans α-cyanoaziridine **3o** in a 1:1:2 ratio, respectively. Compounds **17a** and trans **3o** may result from transformation of the cis isomer **3o**. Benzylideneamines **17a,b** were shown to be identical with authentic samples prepared by reaction of benzaldehyde with the corresponding amine.

Benzylideneisopropylamine (17a): ^{1}H NMR (CCl_4) δ 1.14 (6 H, d, J = 6 Hz, Me_2), 3.50 (1 H, septet, J = 6 Hz, NCH), 7.2–7.5 (3 H, m, meta and para protons), 7.5–7.8 (2 H, m, ortho protons), 8.22 (1 H, s, CH=N); IR (NaCl) 1655 cm^{-1} ($\nu_{C=N}$); mass spectrum, m/e (relative abundance) 147 (M^+, 45), 132 (100), 105 (25), 104 (41), 91 (45), 77 (23), 43 (64).

Benzylidene-*tert*-butylamine (17b): ^{1}H NMR (CCl_4) δ 1.26 (9 H, s, *t*-Bu), 7.2–7.5 (3 H, m, meta and para protons), 7.5–7.8 (2 H, m, ortho protons), 7.16 (1 H, s, CH=N); IR (NaCl) 1640 cm^{-1} ($\nu_{C=N}$).

Acknowledgment. We are indebted to the Belgian Nationaal Fonds voor Wetenschappelijk Onderzoek (National Fund for Scientific Research) for generous financial support to the laboratory.

Registry No. **1a**, 78827-38-0; **1b**, 81803-16-9; **1c**, 87207-61-2; **1d**, 87207-62-3; **1e**, 87207-63-4; **1f**, 87207-64-5; **1g**, 81815-43-2; **1h**, 84300-49-2; **1i**, 87207-65-6; **1l**, 78827-37-9; **1m**, 78827-36-8; **1o**, 78827-43-7; **1p**, 87207-66-7; **1q**, 87207-67-8; **2a**, 87207-68-9; **2**, 87207-69-0; **2k**, 87207-70-3; **3a**, 81803-21-6; **3b**, 81803-22-7; **3c**, 87207-71-4; **3d**, 87207-72-5; **3e**, 87207-73-6; **3f**, 87207-74-7; *cis*-**3g**, 81803-19-2; *trans*-**3g**, 81803-20-5; *cis*-**3h**, 87207-75-8; *trans*-**3h**, 87207-89-4; **3i**, 87207-76-9; **3j**, 87207-77-0; **3k**, 87207-78-1; *cis*-**3l**, 87207-94-1; *trans*-**3l**, 81803-18-1; *cis*-**3m**, 81803-17-0; *trans*-**3m**, 81803-23-8; *cis*-**3o**, 81803-24-9; *trans*-**3o**, 81803-25-0; *cis*-**3p**, 87207-79-2; *cis*-**3q**, 87207-80-5; **4a**, 81803-26-1; **4b**, 81803-27-2; **4c**, 87207-81-6; **4d**, 87207-82-7; **4e**, 87207-83-8; **4f**, 87207-84-9; **5a**, 87207-85-0; **5c**, 87207-86-1; **5d**, 87207-87-2; **5e**, 87207-88-3; **12a**, 87207-91-8; **15a**, 87207-92-9; **15b**, 87207-93-0; **17a**, 6852-56-8; **17b**, 6852-58-0; *N*-allyl-3,3-dimethoxy-2-butylamine, 84393-18-0; 3-methoxy-3-methyl-2-butanone, 36687-98-6; (2,4-dimethyl-1-penten-3-ylidene)isopropylamine, 87207-90-7.

Supplementary Material Available: Physical and spectrometric data of α-chloro and α-bromo ketimines **1** and **2** (Table I); spectrometric properties of α-cyanoaziridines **3** (Table II); spectrometric data of 1-(*N*-alkyl)aminocyclopropanecarbonitriles **4** (Table III); and ^{13}C NMR data of 1-(*N*-alkyl)aminocyclopropanecarbonitriles **4** (Table IV) (9 pages). Ordering information is given on any current masthead page.

Chemistry of β-Triketones. 1. Structure of Schiff Base Intermediates of 2-Acyl-1,3-indandiones[1]

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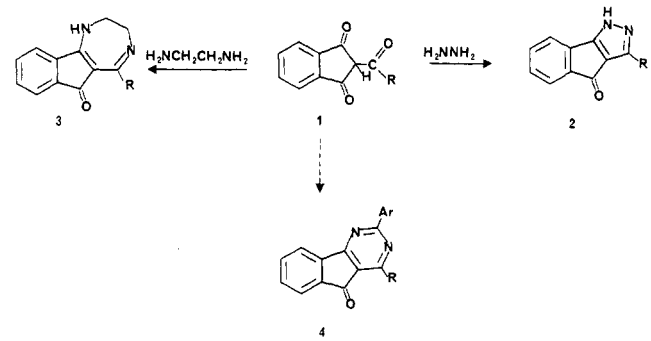
Schiff base formation has been shown to occur preferentially at the exocyclic carbonyl of 2-acyl-1,3-indandiones (**1**). The resulting addition product exists either as an open-chain compound (**10–16**) or as a cyclic hemiketal (**19–27**). The size of the acyl substituent appears to influence the structure of the Schiff bases.

The 2-acyl-1,3-indandiones (**1**) have served as a useful synthon for the preparation of a variety of tricyclic heterocycles. The reaction of **1** with hydrazine results in the formation of indenopyrazoles (**2**),[2-7] while the addition of ethylenediamine and *o*-phenylenediamine gives rise to indenodiazepines (**3**).[8-9] A series of 2-benzylidene-1,3-indandiones were used and condensed with benzamidines, and the indenopyrimidines (**4**) have been prepared.[10]



We have been interested in this area for some time, both for its synthetic utility for the preparation of tricyclic heterocycles and from the theoretical standpoint as to the site of initial addition of the nucleophile. Since most of the reagents previously used have led to symmetrical final

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