"*tert*-Amino Effect" in Heterocyclic Synthesis. Formation of *N*-Heterocycles by Ring-Closure Reactions of Substituted 2-Vinyl-*N*,*N*-dialkylanilines

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2-Vinyl-*N*,*N*-dialkylanilines react thermally in polar solvents and/or in the presence of Lewis acids via [1,5] or [1,6] hydrogen transfer followed by C–C bond formation to give heterotricyclic compounds. The reaction depends on the type of *N*,*N*-dialkylamino group and on the type and position of substituents of the vinyl moiety. 1-Pyrrolidinyl butenedioate **5a** and (1-pyrrolidinyl)benzeneacetonitrile **7a** undergo a thermal rearrangement to the pyrrolo[1,2-*a*]indoles **12a,b** and **13a,b**, respectively, while the 1-piperidinyl and 4-morpholinyl butenedioates **5b,c** and the (4-morpholinyl)benzeneacetonitrile **7c** do not react. The (1-piperidinyl)benzeneacetonitrile **7b** yields in refluxing toluene in the presence of zinc chloride the pyrido[1,2-*a*]indole **14b** and, by HCN elimination, pyrido[1,2-*a*]indole **15b**. Under these conditions the *cis*- and *trans*-pyrrolo[1,2-*a*]indoles **13a** and **13b** also eliminate HCN to give **15a**. Heating the 1-pyrrolidinyl propanedioate **10** and the 1-pyrrolidinyl, 1-piperidinyl, and 4-morpholinyl propanedinitriles **11a–c** in 1-butanol gives the pyrrolo[1,2-*a*]quinolines **16a,b**, benzo[*c*]quinolizine **17**, and [1,4]oxazino[4,3-*a*]quinoline **18**, respectively. The mechanisms of both types of cyclization, which are examples of the "*tert*-amino effect", are discussed.

Introduction

Previously we have reported that reactions of 3-(1-pyrrolidinyl)thiophenes[1d] and pyrrolidine enamines[2,3] with the electron-deficient acetylene dimethyl acetylenedicarboxylate (DMAD) in protic polar solvents yield pyrrolizine derivatives. It was shown that the Michael adducts of 2-(1-pyrrolidinyl)thiophenes and DMAD react as 1-(1-pyrrolidinyl)-1,3-butadienes to give pyrrolizines by the in situ generation of a 1,5-dipole via a concerted [1,6] hydrogen transfer, followed by a concerted disrotatory electrocyclization of the 6π-electron system.[4] This mode of reaction has also been recently reported by the groups of Speckamp,[5] Pandit,[6] and Grigg.[7]

A number of years ago Meth-Cohn and Suschitzky[8] reviewed the formation of heterocycles by ring closure of ortho-substituted tertiary anilines (the "*tert*-amino effect"). This ring closure can proceed in different modes (1 and 2) dependent on the nature of A=B (Chart I). In their review the authors have only described reactions of aniline derivatives in which A=B has at least one hetero atom, but we felt that this type of reaction might have a wider applicability. The above mentioned conversion of 1-(1-pyrrolidinyl)-1,3-butadienes into pyrrolizines can also be regarded as an example of this type of reaction. The synthesis of 1,3-oxazines by reaction of enamines with trifluoroacetic anhydride, which we found recently,[9] can be regarded as another example.

In this paper we describe the reactions of 2-vinyl-*N*,*N*-dialkylanilines in which one of the double bonds of the 1-(1-dialkylamino)-1,3-butadiene moiety constitutes part of an aromatic ring.

Chart I

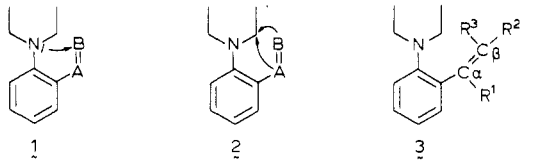

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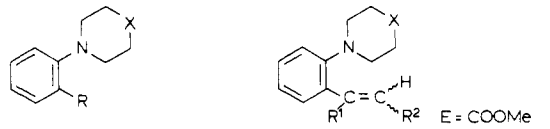
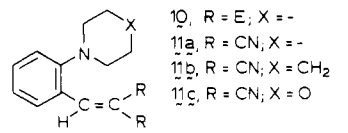
Chart II



4a, R = Br, X = -
4b, R = Br, X = CH_2
4c, R = Br, X = O
6a, R = CH_2CN, X = -
6b, R = CH_2CN, X = CH_2
6c, R = CH_2CN, X = O
8a, R = CHO, X = -
8b, R = CHO, X = CH_2
8c, R = CHO, X = O

5a, $R^1 = R^2 = E$, X = -
5b, $R^1 = R^2 = E$, X = CH_2
5c, $R^1 = R^2 = E$, X = O
7a, $R^1 = CN$, $R^2 = Ph$, X = -
7b, $R^1 = CN$, $R^2 = Ph$, X = CH_2
7c, $R^1 = CN$, $R^2 = Ph$, X = O
9, $R^1 = H$, $R^2 = COOEt$, X = - (E)



10, R = E; X = -
11a, R = CN; X = -
11b, R = CN; X = CH_2
11c, R = CN; X = O

Results[10]

Synthesis of 2-Vinyl-*N*,*N*-dialkylamines. Dimethyl 2-[2-(1-pyrrolidinyl)phenyl]butenedioate (**5a**) was obtained by the addition of 2-(1-pyrrolidinyl)phenylcopper,[11] prepared from [2-(1-pyrrolidinyl)phenyl]magnesium bromide and copper(I) bromide, to DMAD in a yield of 75%.[12] The ^{1}H NMR spectrum of the reaction product shows the absorption of only one vinylic hydrogen atom at δ 6.07, and therefore we concluded that the reaction had proceeded

(1) (a) Laboratory of Organic Chemistry. (b) Laboratory of Chemical Analysis. (c) Laboratory of Chemical Physics. (d) Reinhoudt, D. N.; Geevers, J.; Trompenaars, W. P.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1981**, *46*, 424.

(2) Geevers, J.; Visser, G. W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 251.

(3) Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *Tetrahedron* **1981**, *37*, 3525.

(4) Reinhoudt, D. N.; Visser, G. W.; Verboom, W.; Benders, P. H.; Pennings, M. L. M. *J. Am. Chem. Soc.* **1983**, *105*, 4775.

(5) Speckamp, W. N.; Veenstra, S. J.; Dijkink, J.; Fortgens, R. *J. Am. Chem. Soc.* **1981**, *103*, 4643.

(6) Kanner, C. B.; Pandit, U. K. *Tetrahedron* **1981**, *37*, 3519.

(7) Grigg, R.; Gunaratne, H. Q. N. *Tetrahedron Lett.* **1983**, *24*, 1201.

(8) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211.

(9) Verboom, W.; Reinhoudt, D. N.; Harkema, S.; van Hummel, G. J. *J. Org. Chem.* **1982**, *47*, 3339.

(10) The results of this investigation have been partly published in a preliminary communication. See: Visser, G. W.; Verboom, W.; Benders, P. H.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1982**, 669.

(11) For a recent review see: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(12) In contrast to 2-(1-pyrrolidinyl)benzo[*b*]thiophene, which reacted with DMAD in methanol to afford the 3-vinyl-2-(1-pyrrolidinyl)benzo[*b*]thiophene derivative,[4] 1-(1-pyrrolidinyl)benzene did not react with DMAD, either in the presence of a Lewis acid or thermally or photochemically.

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stereospecifically. Comparison of this value with that of the corresponding vinylic hydrogen atom in the other stereoisomer, which could be obtained by thermal isomerization (vide infra), showed that the stereochemistry of **5a** is *Z*. Starting from 1-(2-bromophenyl)piperidine (**4b**) or 4-(2-bromophenyl)morpholine (**4c**), we obtained dimethyl (*Z*)-2-[2-(1-piperidinyl)- and (*Z*)-2-[2-(4-morpholinyl)phenyl]butenedioates (**5b–c**) in yields of 78% and 34%, respectively (Chart II).

Other 2-vinyl-*N*,*N*-dialkylanilines viz, α-(phenylmethylene)-2-(1-pyrrolidinyl)-, α-(phenylmethylene)-2-(1-piperidinyl)-, and α-(phenylmethylene)-2-(4-morpholinyl)benzeneacetonitriles (**7a–c**) could easily be prepared as *E*/*Z* mixtures by a condensation reaction of 2-(1-pyrrolidinyl)-, 2-(1-piperidinyl)-, and 2-(4-morpholinyl)benzeneacetonitriles (**6a–c**) with benzaldehyde in the presence of sodium ethoxide as a base in ethanol in yields of 88%, 92%, and 80%, respectively.

In order to study the effect of substituents on the reactivity of compounds **3** we were also interested in compounds with only one electron-withdrawing group at the β-position. We therefore prepared ethyl [2-(1-pyrrolidinyl)phenylmethylene]acetate (**9**) by a Wadsworth–Emmons reaction[13] of 2-(1-pyrrolidinyl)benzaldehyde (**8a**) and triethyl phosphonoacetate in the presence of sodium hydride in a yield of 78%. In the ^{1}H NMR spectrum of **9**, the vinylic hydrogen atoms exhibit a coupling constant of 15.9 Hz, therefore we concluded that the stereochemistry of **9** is *E*.

Another class of compounds **3** is that which has two electron-withdrawing groups at the β-position. This type of compounds is readily accessible via a Knoevenagel condensation[14] of substituted benzaldehydes with, for instance, dimethyl malonate[15] (propanedioic acid dimethyl ester) or malonitrile (propanedinitrile). Reaction of aldehyde **8a** with dimethyl malonate and pyrrolidine as a catalyst afforded dimethyl [2-(1-pyrrolidinyl)phenylmethylene]propanedioate (**10**) in a yield of 76%. Horner and Klüpfel[16] used ammonium acetate and acetamide as catalysts for the condensation reaction of substituted benzaldehydes with malonitrile. However, we found that the reaction of 2-(1-pyrrolidinyl)-, 2-(1-piperidinyl)-, and 2-(4-morpholinyl)benzaldehydes (**8a–c**) with malonitrile already proceeded at room temperature in the absence of a catalyst, giving the [2-(1-pyrrolidinyl)-, [2-(1-piperidinyl)-, and [2-(4-morpholinyl)phenylmethylene]propanedinitriles (**11a–c**) in yields of 91%, 89%, and 90%, respectively.

Thermal Rearrangement of 2-Vinyl-*N*,*N*-dialkylanilines. When compound (*Z*)-**5a** was heated in toluene it was completely converted into a mixture of two isomers of (*Z*)-**5a** which were isolated in yields of 54% and 32%, respectively.[17] The major compound exhibited characteristic absorptions in the ^{1}H NMR spectrum at δ 4.65 (dd) and δ 3.63 and 2.72 (AB q) and in the ^{13}C NMR spectrum at δ 72.0 (d), 54.1 (s), and 38.9 (t). The minor compound showed corresponding values in the ^{1}H NMR spectrum at δ 3.79 (dd) and 3.23 and 2.80 (AB q) and in the ^{13}C NMR spectrum at δ 75.1 (d), 55.1 (s), and 44.3 (t). On the basis of the spectral data which were compared with those of the recently published[4] methyl *cis*- and *trans*-2,3,10,10a-tetrahydro-10-(methoxycarbonyl)-1*H*-[1]benzothieno[3,2-*b*]pyrrolizine-10-acetates we concluded that the major reaction product was methyl *cis*-2,3,9,9a-tetrahydro-9-(methoxycarbonyl)-1*H*-pyrrolo[1,2-*a*]indole-9-acetate (**12a**) and the minor reaction product the corresponding trans isomer **12b**.

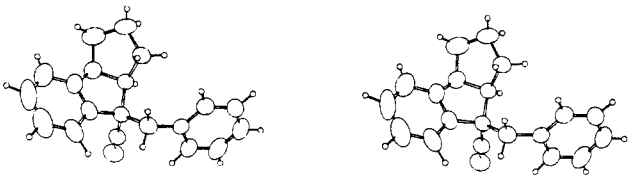
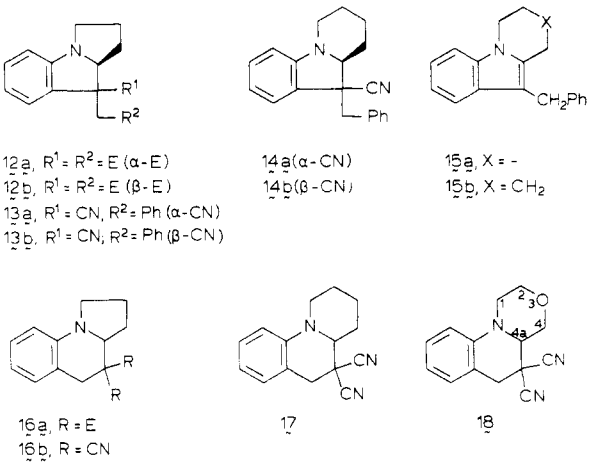


Figure 1. Stereoscopic view of pyrrolo[1,2-*a*]indole **13a**.

Chart III



The solvent appeared to have a large effect on both the rate of the reaction and the stereochemistry of the product formed. Reaction in 1-butanol resulted in the exclusive conversion of **5a** into the cis isomer **12a** which was isolated in a yield of 74%. In the ^{1}H NMR spectrum of the crude reaction mixture no trace of the corresponding trans isomer **12b** could be detected (Chart III).

In order to investigate the scope of this reaction we studied the effect of the position of the substituents at the vinyl group. In compounds **5** the vinyl moiety possesses one electron-withdrawing group (the ester function) at the α position and one at the β position. The benzeneacetonitriles **7**, however, have only an electron-withdrawing group (a cyano group) at the α position. Heating of benzeneacetonitrile **7a** in toluene at 110 °C for 3 days did not give cyclization as followed from ^{1}H NMR spectroscopy; in the spectrum only starting material was detected. However when **7a** was heated in 1-butanol reaction did occur. After column chromatography of the crude reaction mixture, besides starting material (14%) the diastereoisomeric *cis*- and *trans*-2,3,9,9a-tetrahydro-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitriles (**13a**) and (**13b**) were isolated in yields of 44% and 42%, respectively. Both compounds exhibited corresponding spectroscopic data as the above described pyrrolo[1,2-*a*]indoles **12**. Since the pyrrolo[1,2-*a*]indoles **13** differ from compounds **12** by other substituents at C-9 the definite assignment of the stereochemistry of **13** could not be made on the basis of NMR spectroscopy. However, the structure proof was given by single-crystal X-ray analysis of **13a** which shows that **13a** indeed has the cis configuration (Figure 1). The presence of zinc chloride accelerated the reaction considerably. Heating of a mixture of **7a** and zinc chloride in acetonitrile yielded after chromatography, besides some starting material (8%), the pyrrolo[1,2-*a*]indoles **13a** and

(13) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.
(14) For a review see: Jones, G. *Org. React.* **1967**, *15*, 204.
(15) For reviews on the chemistry of malonitrile see: Fatiadi, A. J. *Synthesis* **1978**, 165 and **1978**, 241.
(16) Horner, L.; Klüpfel K. *Liebigs Ann. Chem.* **1955**, *591*, 69.
(17) After reaction for several hours an aliquot was taken. The ^{1}H NMR spectrum revealed the presence of (*E*)-**5a** as followed from the signal of the vinylic hydrogen atom at δ 6.78 (s). After completion of the reaction in the ^{1}H NMR spectrum of the crude reaction mixture this absorption had disappeared.

13b in yields of 47% and 12%, respectively.[18]

Heating of **9**, which has only one electron-withdrawing group at the β position, in refluxing 1-butanol for 10 days or in refluxing acetonitrile in the presence of zinc chloride for 3 days gave only starting material. In the ^{1}H NMR spectrum no trace of a ring-closed product could be detected. This result agrees with that of the Michael adducts prepared from (pseudo) 1-pyrrolidinyl enamines and methyl propiolate, with which also no cyclization could be achieved.[3,4]

When the yellow propanedioate **10**, which possesses two electron-withdrawing groups at the β position, was heated in 1-butanol a white isomer of **10** was obtained in a yield of 67%. In the ^{1}H NMR spectrum of the product a characteristic multiplet at δ 3.85–3.65 corresponding with one hydrogen atom was present. The ^{13}C NMR spectrum exhibited, among others, absorptions at δ 62.0 (d), 53.2 (s), and 36.9 (t). On the basis of these and other spectroscopic data we concluded that the reaction product was dimethyl 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarboxylate (**16a**).

The malonitrile adduct **11a** reacted similarly in refluxing 1-butanol to give 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]-quinoline-4,4-dicarbonitrile (**16b**) in a yield of 82%. When the reaction was performed in refluxing toluene a considerable solvent effect was observed. In this case the reaction time is 35 h compared with 2 h in refluxing 1-butanol.

As mentioned above the reaction of 1-(1-pyrrolidinyl)-enamines with DMAD in methanol afforded pyrrolizines.[1-3] Starting from 1-(1-piperidinyl)- and 1-(4-morpholinyl)enamines a corresponding reaction could not be accomplished. However, Meth-Cohn and Suschitzky[8] did give some examples of ring-closure reactions in systems containing these dialkylamino groups. Therefore we have investigated the influence of the structure of the amino moiety on the reactions described above.

Both (*Z*)-**5b** and (*Z*)-**5c** gave only rise to a partial *Z* to *E* isomerization upon heating in toluene or 1-butanol for 7 days as followed from the comparison of the absorptions of the vinylic hydrogen atoms at δ 6.73 and 6.75, respectively, with the absorptions of the corresponding *Z* isomers. In both cases the Lewis acid zinc chloride (in toluene) did not affect the reaction whereas the use of boron trifluoride etherate in the case of (*Z*)-**5b** resulted in decomposition of the starting material. The same result was obtained using acetic acid as a solvent. Starting from **7c** cyclization did also not take place both in refluxing toluene in the presence of zinc chloride and in refluxing acetic acid for 12 days.

The piperidine benzeneacetonitrile **7b** did not react in acetonitrile in the presence of zinc chloride at 81 °C for 3 days or in refluxing 1-butanol for 6 days. However, heating of a mixture of **7b** and zinc chloride in toluene gave, after chromatography, in addition to starting material (5%) and 6,7,8,9,9a,10-hexahydro-10-(phenylmethyl)-pyrido[1,2-*a*]indole-10-carbonitrile (**14**; 11%) another compound in a yield of 26%. From the spectroscopic data the assignment of the stereochemistry of **14** as compared with the corresponding values of the diastereoisomeric **13a** and **13b** is difficult. On the basis of the different rates of elimination of HCN from **13a** and **13b** we are tempted to conclude that the stereochemistry of this product is trans (**14b**) (vide infra).

The elemental composition of the other reaction product (M^+ $C_{19}H_{19}N$) indicated loss of HCN from the starting material. The ^{1}H NMR spectrum showed a signal at δ 4.04 (s, 2 H) while the characteristic (double doublet) absorption for the NCH hydrogen atom was absent. Furthermore in the ^{13}C NMR spectrum the corresponding NCH absorption was lacking. However, in the area up to δ 100 two additional signals are present as compared with the ^{13}C NMR spectrum of **14b**. On the basis of these data we concluded that the compound was 6,7,8,9-tetrahydro-10-(phenylmethyl)pyrido[1,2-*a*]indole (**15b**).

The unexpected formation of **15b** led us to investigate whether HCN elimination was also possible from **13a,b** and **14b**. Heating a mixture of the *cis*-pyrrolo[1,2-*a*]indole **13a** and zinc chloride in toluene gave rise to the formation of 2,3-dihydro-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole (**15a**) which was isolated in a yield of 61%. When the starting material was *trans*-pyrrolo[1,2-*a*]indole **13b**, the same reaction product was formed, however, after a much longer reaction time, i.e., 70 h. Heating a mixture of **14b** and zinc chloride in toluene at 110 °C for 3 weeks gave no HCN elimination.

The piperidinyl and morpholinyl malononitrile adducts **11b–c** reacted in a similar way as the corresponding pyrrolidinyl derivative **11a** to give 2,3,4,4a,5,6-hexahydro-1*H*-benzo[*c*]quinolizine-5,5-dicarbonitrile (**17**) and 1,2,4,4a,5,6-hexahydro[1,4]oxazino[4,3-*a*]quinoline-5,5-dicarbonitrile (**18**) in yields of 78% and 84%, respectively. The 80-MHz ^{1}H NMR spectrum of **18** exhibited a complicated multiplet in the range δ 4.5–2.8 corresponding with nine hydrogen atoms from which no definite structural assignment could be derived. Therefore a 500-MHz ^{1}H NMR spectrum was recorded, together with some specifically homonuclear decoupled spectra.[19] The relevant part of the spectrum is shown in Figure 2 while the assignments are summarized in Table I. The coupling constants between proton 4a and both protons 4 clearly indicate that proton 4a is in the axial position.[20]

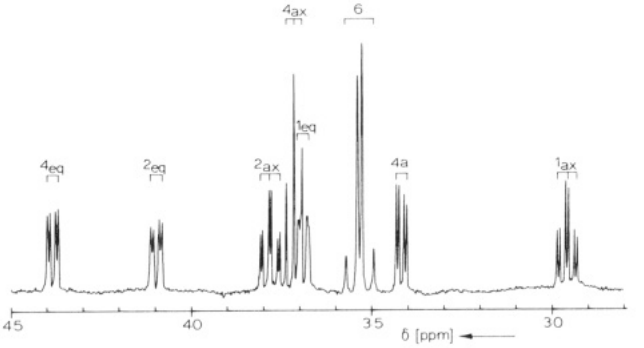


Figure 2. 500-MHz ^{1}H NMR spectrum of **18** (range δ 4.5–2.8).

Table I. ^{1}H NMR Spectral Data of **18** (Range δ 4.5–2.8)[a]

position	chemical shift, δ	coupling constant (J), Hz
1_{eq}	3.69	1_{eq}-1_{ax}, −11.9; 1_{eq}-2_{eq}, ~0; 1_{eq}-2_{ax}, 2.1
1_{ax}	2.96	1_{ax}-2_{eq}, 3.8; 1_{ax}-2_{ax}, 12.2
2_{eq}	4.10	2_{eq}-2_{ax}, −11.6
4_{eq}	4.39	4_{eq}-4_{ax}, −11.3; 4_{eq}-4a, 3.7
4_{ax}	3.72	4_{ax}-4a, 10.8
4a	3.42	
6	3.52; 3.55	6-6, 16.2

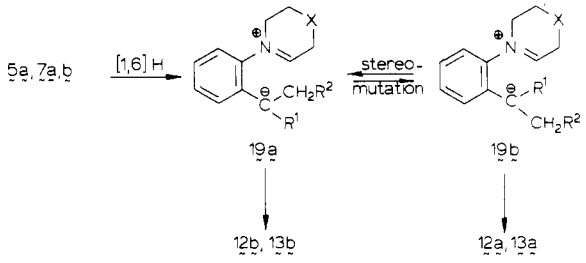
[a] Solvent $CDCl_3$; reference standard Me_4Si.

(18) No trace of a HCN eliminated product was detected in the ^{1}H NMR spectrum of the crude reaction mixture (vide infra).

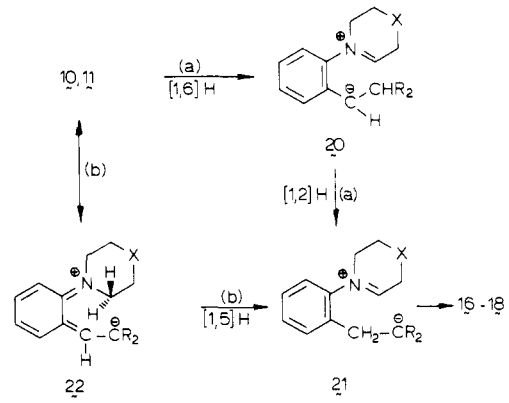
(19) The 500-MHz ^{1}H NMR spectra were recorded at the Dutch national 500/200 MHz HF-NMR facility at Nijmegen with a Bruker WM-500 spectrometer.

(20) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969.

Scheme I



Scheme II



Discussion

The formation of **12–14** can be explained by two consecutive reactions as depicted in Scheme I. The first step comprises a thermal antarafacial [1,6][21] hydrogen shift via a helical transition state producing the 1,5-dipole **19a**, which depending on the structure and the conditions may (partly) stereomutate to the 1,5-dipole **19b**. Both 1,5-dipoles can undergo a concerted disrotatory electrocyclization of the 6π-electron system with formation of the products **12–14**. In our previous paper[4] we have discussed this mechanism extensively starting from dimethyl (*E*)- and (*Z*)-[2-(1-pyrrolidinyl)benzo[*b*]thien-3-yl]-2-butenedioate which possess a similar type of 1-(1-dialkylamino)-1,3-butadiene moiety. In that particular case we found that there was no interconversion between the *E* and *Z* isomers and that for the *E* isomer the rate of cyclization was 5.2 times faster. However, in the examples described in the present study we did observe interconversion under the reaction conditions so that it is not possible to prove if only one or both of the isomers gave rise to cyclization.

We have also proven that the [1,6] hydrogen transfer comprises the rate-determining step in the conversion of 1-(1-pyrrolidinyl)-1,3-butadienes into pyrrolizines. This means that groups stabilizing the 1,5-dipole will lower the activation energy. Stabilization of the "positive end" of the 1,5-dipole is mainly dependent on the efficiency of the overlap between the lone pair of the nitrogen atom and the π-system of the aromatic ring. Effenberger et al.[22] have demonstrated with HMO π-electron density chemical shift correlations that in (dialkylamino)benzenes the donor potential decreases in the series pyrrolidine > piperidine > morpholine. This effect may be the reason why if starting from **7a** the reaction is much faster than for **7b**, while in the case of the morpholino derivatives we find no reaction at all. Furthermore, in the case of the morpholino derivatives **5c** and **7c** the positive part of a formed 1,5-dipole **19** will be destabilized by the inductive effect of the oxygen atom.

The stabilization of the "negative end" of the 1,5-dipole requires the presence of one electron-withdrawing group (E or CN) at the appropriate carbon atom. This explains why **9** is not reactive and why the reactivity of **10** and **11** differs from compounds **5** and **7**. The formation of **16–18** by reaction of **10,11** may be rationalized in two different ways as depicted in Scheme II. In reaction path a an intramolecular antarafacial [1,6] hydrogen shift of one of the α-methylene protons adjacent to nitrogen gives the 1,5-dipole **20** which tautomerizes to the more stable zwitterion **21**. Subsequently intramolecular addition of the carbanion to the iminium double bond gives rise to compounds **16–18**. In reaction path b a suprafacial [1,5] hydrogen shift of one of the α-methylene protons adjacent to nitrogen in **10,11**, visualized as the mesomeric form **22**, will lead to **21**, which ultimately gives ring closure to **16–18**. Reaction path a corresponds to the pathway proposed by Meth-Cohn and Suschitzky[8] for other compounds **2**. The difference between the both reaction pathways a and b is that either a [1,6][21] or a [1,5] hydrogen shift takes place. It is known[23] that an antarafacial [1,7] hydrogen shift in hepta-1,3,5-trienes, which corresponds to a [1,6] hydrogen shift in our case, will be faster than a suprafacial [1,5] hydrogen shift. However, in compounds **10,11** a [1,6] hydrogen shift is very unlikely because of the lack of stabilization of the "negative end" of the 1,5-dipole, a situation similar to compound **9**.

We have obtained strong evidence that the reaction proceeds via pathway b because when the reaction of **11a** was performed in 1-deuterio-1-butanol no incorporation of deuterium was detected in the ultimate product. This result can only be explained by a concerted thermal [1,5] hydrogen shift as proposed in reaction path b. This virtually eliminates reaction path a since this would require a concerted [1,2] hydrogen shift in a carbanion as the second step. It is known that such rearrangements, when occurring, appear to be stepwise.[25]

From this mechanism it also follows that in apolar solvents (like toluene) the rate of the reaction will be lower than in polar solvents because the intermediate dipoles are less stabilized by solvation.

In contrast to the compounds **5** and **7** both the pyrrolidino and piperidino[25] and morpholino derivative **11a**, **11b**, and **11c** cyclize. This may be due to the fact that in **21** the negative charge is very well stabilized by the *two* electron-withdrawing groups R^2. This effect may compensate for the above described less effective stabilization of the iminium group in the morpholine ring which, however, is still reflected in a longer reaction time.

The zinc chloride promoted HCN elimination of pyrrolo[1,2-*a*]indole **13a** is about 3 times faster than that starting from the isomeric **13b**. This may be explained by the fact that there is a difference in dihedral angle of the hydrogen atom involved and the cyano moiety between **13a** and **13b**. The X-ray analysis of **13a** showed that this angle in **13a** is ~30° while in **13b** this angle will be close to 90°. The latter value has been estimated on the basis of the dihedral angle between the hydrogen atom and the methylene carbon atom of the phenylmethyl group to be

(21) This shift is electronically equivalent with a [1,7] hydrogen shift in the all-carbon system since the lone pair of the nitrogen atom contributes 2 π electrons.

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(25) Compound **11a** as well as **11b** were completely converted within 2 h in refluxing 1-butanol. We have not carried out the reaction at lower temperature in order to determine a difference if any in the rate of the reaction.

95° in **13a**. When these values are compared, it will be clear that in the case of **13b** the elimination will be slower because the hydrogen atom and the cyano group are almost perpendicular, which is a very unfavorable situation for the elimination process. A similar reasoning might explain the difference in reactivity between **14a** and **14b**.

Conclusion

In our present study we have demonstrated that 2-vinyl-*N*,*N*-dialkylanilines are interesting precursors for the facile preparation of several classes of heterocyclic compounds. Hitherto, several of them could only be obtained in low yield or via multistep procedures, e.g., the 6,7,8,9,9a,10-hexahydropyrido[1,2-*a*]indole[26] and the 1,2,4,4a,5,6-hexahydro[1,4]oxazino[4,3-*a*]quinoline[27] skeletons are virtually unknown. Furthermore we have proven that the "*tert*-amino effect" is also applicable to systems **3** when A=B is C=C. Depending on the nature of the substituents R^1, R^2, and R^3 either five- or six-membered heterocyclic rings can be obtained.

Experimental Section

Melting points were determined with a Reichert melting point apparatus and are uncorrected. ^1H NMR spectra ($CDCl_3$) were recorded with a Bruker WP-80 spectrometer and ^{13}C NMR spectra ($CDCl_3$) were recorded with a Varian XL-100 spectrometer (Me_4Si as an internal standard). Mass spectra were obtained with a Varian MAT 311A spectrometer and IR spectra with a Perkin-Elmer 257 spectrophotometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under supervision of W. J. Buis and G. J. Rotscheid.

The 2-(dialkylamino)benzaldehydes **8a–c** were prepared as described.[28] Dimethyl acetylenedicarboxylate (DMAD) refers to Aldrich reagent and was distilled before use. Most other compounds used were commercially available unless stated otherwise. All reactions were carried out under a nitrogen atmosphere.

General Procedure for the Dialkylation of 2-Bromoaniline and 2-Aminobenzeneacetonitrile. A solution of 2-bromoaniline (8.60 g, 50 mmol) or 2-aminobenzeneacetonitrile[29] (6.60 g, 50 mmol), a dihalogeno compound (50 mmol), and ethyldiisopropylamine (15.51 g, 120 mmol) in 60 mL of toluene was heated at 110 °C. When the reaction was complete as followed from TLC, upon cooling the salts were filtered off. The filtrate was washed with water (3 × 50 mL) and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue was distilled except for in the case of **6c**.

1-(2-Bromophenyl)pyrrolidine (4a) was prepared by reaction of 2-bromoaniline with 1,4-dibromobutane (10.80 g, 50 mmol) for 20 h: yield, 85%; bp 100 °C (0.8 mm); n^{20}_D 1.6060; ^1H NMR δ 7.50 (dd, 1 H, J_{ortho} = 7.2 Hz and J_{meta} = 1.5 Hz, Ar H), 7.3–6.6 (m, 3 H, Ar H), 3.5–3.1 (m, 4 H, NCH_2), 2.1–1.7 (m, 4 H, CH_2); ^{13}C NMR δ 148.4 (s, Ar C-1), 134.3, 127.5, 121.0 and 117.7 (d, Ar C), 113.5 (s, Ar C-2), 51.0 (t, NCH_2), 25.0 (t, CH_2); mass spectrum, *m/e* 225.013 (M^+, calcd for $C_{10}H_{12}{}^{79}BrN$, 225.015).

1-(2-Bromophenyl)piperidine (4b) was prepared by reaction of 2-bromoaniline with 1,5-dibromopentane (11.50 g, 50 mmol) for 25 h: yield, 72%; bp 110–111 °C (1.2 mm); n^{20}_D 1.5782; ^1H NMR δ 7.52 (dd, 1 H, J_{ortho} = 7.7 Hz and J_{meta} = 1.6 Hz, Ar H), 7.4–6.7 (m, 3 H, Ar H), 3.1–2.75 (m, 4 H, NCH_2), 1.9–1.4 (m, 6 H, CH_2); ^{13}C NMR δ 151.4 (s, Ar C-1), 133.5, 127.9, 123.6 and 120.8 (d, Ar C), 119.9 (s, Ar C-2), 53.2 (t, NCH_2), 26.2 (t, (NCH_2CH_2), 24.2 (t, CH_2); mass spectrum, *m/e* 239.028 (M^+, calcd for $C_{11}H_{14}{}^{79}BrN$, 239.031).

4-(2-Bromophenyl)morpholine (4c) was prepared by reaction of 2-bromoaniline with 1,1′-oxybis[2-bromoethane][30] (11.60 g, 50 mmol) for 24 h. After distillation the product solidified on standing: yield, 53%; bp 97–100 °C (0.5 mm); mp 65–66.5 °C (diisopropyl ether); ^1H NMR δ 7.7–6.7 (m, 4 H, Ar H), 4.0–3.6 (m, 4 H, OCH_2), 3.15–2.8 (m, 4 H, NCH_2); ^{13}C NMR δ 150.1 (s, Ar C-1), 133.6, 128.1, 124.4 and 120.6 (d, Ar C), 119.6 (s, Ar C-2), 67.0 (t, OCH_2), 51.9 (t, NCH_2); mass spectrum, *m/e* 241.009 (M^+, calcd for $C_{10}H_{12}N^{79}BrO$, 241.010).

Anal. Calcd for $C_{10}H_{12}NBrO$ (M_r 242.120): C, 49.61; H, 5.00; N, 5.79. Found: C, 49.64; H, 4.94; N, 5.74.

2-(1-Pyrrolidinyl)benzeneacetonitrile (6a) was prepared by reaction of 2-aminobenzeneacetonitrile with 1,4-dibromobutane (10.80 g, 50 mmol) for 4 h. After distillation the compound solidified on standing: yield, 76%; bp 133–134 °C (1.0 mm); mp 49–49.5 °C [petroleum ether (bp 60–80 °C)]; ^1H NMR δ 7.4–6.8 (m, 4 H, Ar H), 3.70 (s, CH_2CN), 3.25–2.85 (m, 4 H, NCH_2), 2.1–1.7 (m, 4 H, CH_2); ^{13}C NMR δ 148.8 (s, Ar C-2), 129.7, 128.6, 121.8 and 118.0 (d, Ar C), 122.7 (s, Ar C-1), 118.6 (s, CN), 51.8 (t, NCH_2), 24.9 (t, CH_2), 21.0 (t, CH_2CN); IR (KBr) 2248 (CN) cm^{-1}; mass spectrum, *m/e* 186.114 (M^+, calcd, 186.116).

Anal. Calcd for $C_{12}H_{14}N_2$ (M_r 186.258): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.24; H, 7.70; N, 14.96.

2-(1-Piperidinyl)benzeneacetonitrile (6b) was prepared by reaction of 2-aminobenzeneacetonitrile with 1,5-dibromopentane (11.50 g, 50 mmol) for 18 h. After distillation the product solidified on standing: yield, 78%; bp 110–112 °C (0.35 mm); mp 35–36 °C [petroleum ether (bp 60–80 °C)]; ^1H NMR δ 7.6–7.0 (m, 4 H, Ar H), 3.81 (s, CH_2CN), 3.0–2.65 (m, 4 H, NCH_2), 1.9–1.4 (m, 6 H, CH_2); ^{13}C NMR δ 152.3 (s, Ar C-2), 129.1, 128.8, 124.1 and 120.9 (d, Ar C), 126.1 (s, Ar C-1), 118.7 (s, CN), 54.0 (t, NCH_2), 26.5 (t, NCH_2CH_2), 24.1 and 19.3 (t, CH_2 and CH_2CN); IR (KBr) 2248 (CN) cm^{-1}; mass spectrum, *m/e* 200.131 (M^+, calcd, 200.131).

Anal. Calcd for $C_{13}H_{16}N_2$ (M_r 200.285): C, 77.96; H, 8.05; N, 13.99. Found: C, 78.05; H, 8.17; N, 13.94.

2-(4-Morpholinyl)benzeneacetonitrile (6c) was prepared by reaction of 2-aminobenzeneacetonitrile with 1,1′-oxybis[2-chloroethane] (7.15 g, 50 mmol) for $5^1/_2$ days. After removal of the solvent under reduced pressure the resulting solid was triturated with diethyl ether to afford **6c**: yield, 52%; mp 106–107 °C (diethyl ether); ^1H NMR δ 7.6–7.1 (m, 4 H, Ar H), 4.0–3.7 (m, 4 H, OCH_2), 3.83 (s, 2 H, CH_2CN), 3.0–2.75 (m, 4 H, NCH_2); ^{13}C NMR δ 150.7 (s, Ar C-2), 129.5, 129.2, 125.1 and 121.3 (d, Ar C), 126.5 (s, Ar C-1), 118.4 (s, CN), 67.2 (t, OCH_2), 52.9 (t, NCH_2), 19.5 (t, CH_2CN); IR (KBr) 2242 (CN) cm^{-1}; mass spectrum, *m/e* 202.110 (M^+, calcd, 202.111).

Anal. Calcd for $C_{12}H_{14}N_2O$ (M_r 202.258): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.08; H, 6.89; N, 13.88.

General Procedure for the Formation of Dimethyl (*Z*)-2-[2-(1-Pyrrolidinyl)-, (*Z*)-2-[2-(1-Piperidinyl)-, and (*Z*)-2-[2-(4-Morpholinyl)phenyl]butenedioates (5a–c). To a suspension of copper(I) bromide (1.43 g, 10 mmol) in 30 mL of tetrahydrofuran was added 5 mL of a 2.0 M solution of lithium bromide in the same solvent. To the resulting solution of $LiCuBr_2$ was added a Grignard solution (10 mmol, prepared from **4a–c** and magnesium) in 20 mL of tetrahydrofuran at −50 °C. Stirring was continued during 15 min at −50 °C after which a solution of DMAD (1.42 g, 10 mmol) in 5 mL of tetrahydrofuran was added at this temperature. The temperature of the reaction mixture was gradually raised to 0 °C at which temperature stirring was continued for 2 h. The products were isolated by pouring the reaction mixture into a saturated aqueous solution (75 mL) of NH_4Cl containing some NaCN (3 g) and extraction with chloroform (3 × 35 mL). The combined extracts were washed with water and dried with $MgSO_4$. After removal of the solvent under reduced pressure in the cases of **5a–b** the residue was purified by column chromatography [alumina (neutral, V), chloroform/petroleum ether (bp 60–80 °C), 1:2] to give the pure products. In the case of **5c** removal of the solvent yielded a solid which after trituration with ethanol gave the pure compound.

5a: yield, 75%; oil; ^1H NMR δ 7.5–7.2 (m, 2 H, Ar H), 7.1–6.8 (m, 2 H, Ar H), 6.07 (s, 1 H, =CH), 3.81 and 3.77 (s, 3 H, OCH_3), 3.25–3.0 (m, 4 H, NCH_2), 2.05–1.75 (m, 4 H, CH_2); ^{13}C NMR δ 167.8 and 165.7 (s, C=O), 148.4 and 147.8 (s, Ar C-2 and =CE),

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130.3, 129.9, 120.7, 119.7 and 116.5 (d, Ar C and =CHE), 125.6 (s, Ar C-1), 52.3 and 51.8 (q, OCH_3), 51.8 (t, NCH_2), 25.0 (t, CH_2); IR (NaCl) 1715 (C=O) cm^{-1}; mass spectrum, m/e 289.129 (M^+, calcd for $C_{16}H_{19}NO_4$, 289.131).

5b: yield, 78%; oil; ^1H NMR δ 7.5–6.9 (m, 4 H, Ar H), 6.38 (s, 1 H, =CH), 3.80 and 3.78 (s, 3 H, OCH_3), 2.9–2.7 (m, 4 H, NCH_2), 1.8–1.4 (m, 6 H, CH_2); ^{13}C NMR δ 167.3 and 165.5 (s, C=O), 153.0 (s, Ar C-2), 146.4 (s, =CE), 131.8 (s, Ar C-1), 130.8, 130.3, 123.6, 122.4 and 120.0 (d, Ar C and =CHE), 53.7 (t, NCH_2), 51.9 (q, OCH_3), 25.6 (t, NCH_2CH_2), 23.9 (t, CH_2); IR (NaCl) 1718 (C=O) cm^{-1}; mass spectrum, m/e 303.148 (M^+, calcd for $C_{17}H_{21}NO_4$, 303.147).

5c: yield, 34%; mp 140.5–142 °C (diisopropyl ether); ^1H NMR δ 7.6–7.0 (m, 4 H, Ar H), 6.36 (s, 1 H, =CH), 3.82 and 3.78 (s, 3 H, OCH_3), 3.9–3.65 (m, 4 H, OCH_3), 3.0–2.75 (m, 4 H, NCH_2); ^{13}C NMR δ 167.2 and 165.2 (s, C=O), 151.2 (s, Ar C-2), 146.1 (s, =CE), 131.6 (s, Ar C-1), 131.0, 130.7, 124.2, 122.9 and 119.6 (d, Ar C and =CHE), 66.5 (t, OCH_2), 52.4 (t, NCH_2), 52.1 and 51.9 (q, OCH_3); IR (KBr) 1727 (C=O) cm^{-1}; mass spectrum, m/e 305.127 (M^+, calcd, 305.126).

Anal. Calcd for $C_{16}H_{19}NO_5$ (M_r 305.335): C, 62.94; H, 6.27; N, 4.59. Found: C, 62.91; H, 6.10; N, 4.51.

General Procedure for the Preparation of α-(Phenylmethylene)-2-(1-pyrrolidinyl)-, α-(Phenylmethylene)-2-(1-piperidinyl)-, and α-(Phenylmethylene)-2-(4-morpholinyl)-benzeneacetonitriles (7a–c). Sodium (0.5 g, 22 mmol) was dissolved in 35 mL of ethanol. To the resulting solution of sodium ethoxide **6a–c** (5 mmol) was added at room temperature. After the mixture stirred for 5 min, benzaldehyde (0.75 g, 7.1 mmol) was added to the reaction mixture which was subsequently heated at 78.5 °C for 2–3 h. After the mixture cooled, water (5 mL) was added and the solvents were removed under reduced pressure. The residue was suspended in 50 mL of chloroform, washed with water, and dried with $MgSO_4$. After removal of the solvent under reduced pressure in the cases of **7a–b** the residue was purified by column chromatography [silica gel, chloroform/petroleum ether (bp 60–80 °C), 2:1] to afford the pure **7a–b** as yellow oils as a mixture of isomers which were not separated further. In the case of **7c** removal of the solvent yielded a solid which after trituration with diisopropyl ether gave one isomer of **7c** as a yellow solid in a yield of 45%. The filtrate, dissolved in chloroform containing 10% ethyl acetate, was passed through a short column of silica gel to give a E/Z mixture of **7c** (35%) as a yellow oil as followed from TLC. The E/Z mixture of **7c** showed the same ^1H NMR spectrum as the single isomer.

7a: yield, 88%; ^1H NMR δ 7.9–6.7 (m, 10 H, Ar H and =CH), 3.4–3.0 (m, 4 H, NCH_2), 2.0–1.7 (m, 4 H, CH_2); IR (NaCl) 2208 (CN) cm^{-1}; mass spectrum, m/e 274.145 (M^+, calcd for $C_{19}H_{18}N_2$, 274.147).

7b: yield, 92%; ^1H NMR δ 8.1–7.8 (m, 1 H, Ar H), 7.7–6.9 (m, 9 H, Ar H and =CH), 3.1–2.8 (m, 4 H, NCH_2), 2.0–1.4 (m, 6 H, CH_2); IR (NaCl) 2202 (CN) cm^{-1}; mass spectrum, m/e 288.162 (M^+, calcd for $C_{20}H_{20}N_2$, 288.163).

7c: mp 140–141.5 °C (diisopropyl ether); ^1H NMR δ 8.1–7.8 (m, 1 H, Ar H), 7.7–7.0 (m, 9 H, Ar H and =CH), 4.0–3.7 (m, 4 H, OCH_2), 3.2–2.9 (m, 4 H, NCH_2); ^{13}C NMR δ 150.5 (s, Ar C-2), 144.8 (d, =CH), 133.7 and 130.8 (s, Ar C-1 and Ph C-1), 130.2, 128.9, 128.8, 123.8 and 119.8 (d, Ar C), 117.7 (s, CN), 111.0 [s, =*C*(CN)], 66.8 (t, OCH_2), 52.1 (t, NCH_2); IR (KBr) 2209 (CN) cm^{-1}; mass spectrum, m/e 290.143 (M^+, calcd, 290.142).

Anal. Calcd for $C_{19}H_{18}N_2O$ (M_r 290.367): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.45; H, 6.31; N, 9.49.

(*E*)-Ethyl [2-(1-Pyrrolidinyl)phenylmethylene]acetate (9). Triethylphosphonoacetate (4.48 g, 20 mmol) was added dropwise to a slurry of 80% sodium hydride (0.6 g, 20 mmol) in 20 mL of dry benzene at 20 °C. After the addition the solution was stirred for 1 h at room temperature. Thereupon **8a** (3.50 g, 20 mmol) was added dropwise to the solution. During the addition the temperature rose to about 40 °C. After stirring for 1 h at room temperature the reaction mixture was poured into water (50 mL). After separation of the layers the aqueous layer was extracted with chloroform (3 × 50 mL). The combined extracts were washed with water and dried with $MgSO_4$. The solvents were evaporated under reduced pressure and the residue, dissolved in chloroform, was passed through a short column of silica gel. The chloroform was removed to give **9** as an oil in 78% yield. Compound **9** could not be crystallized from organic solvents. ^1H NMR δ 8.04 (d, 1 H, J = 15.9 Hz, =CH), 7.5–7.1 (m, 2 H, Ar H), 6.95–6.7 (m, 2 H, Ar H), 6.23 [d, 1 H, J = 15.9 Hz, =C($COOC_2H_5$)H], 4.25 (q, 2 H, J = 7.2 Hz, OCH_2), 3.5–3.1 (m, 4 H, NCH_2), 2.2–1.8 (m, 4 H, CH_2), 1.33 (t, 3 H, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR δ 167.3 (s, C=O), 149.8 (s, Ar C-2), 144.6, 130.2, 128.7, 119.1, 116.0 and 115.3 (d, Ar C and =CH), 124.4 (s, Ar C-1), 60.1 (t, OCH_2), 52.4 (t, NCH_2), 25.4 (t, CH_2), 14.4 (q, OCH_2CH_3); IR (NaCl) 1702 (C=O) cm^{-1}; mass spectrum, m/e 245.141 (M^+, calcd for $C_{15}N_{19}NO_2$, 245.142).

Dimethyl [2-(1-Pyrrolidinyl)phenylmethylene]propanedioate (10). A solution of **8a** (1.75 g, 10 mmol), dimethyl malonate (1.32 g, 10 mmol), and three drops of pyrrolidine in 15 mL of benzene was refluxed for 18 h. After evaporation of the benzene under reduced pressure, the residue, dissolved in chloroform containing 10% ethyl acetate, was passed through a short column of silica gel. The solvents were removed and the resulting solid purified by trituration with methanol yielding pure **10** as light yellow crystals: yield, 76%; mp 92–93 °C (methanol); ^1H NMR δ 8.02 (s, 1 H, =CH), 7.4–7.15 (m, 2 H, Ar H), 6.9–6.7 (m, 2 H, Ar H), 3.83 and 3.75 (s, 3 H, OCH_3), 3.45–3.2 (m, 4 H, NCH_2), 2.1–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 166.9 and 164.9 (s, C=O), 150.0 (s, Ar C-2), 145.3 (d, =CH), 130.6, 129.3, 118.3, 114.4 (d, Ar C), 122.4 [s, Ar C-1 and =C(E)], 52.3 (t and q, NCH_2 and OCH_3), 25.6 (t, CH_2); IR (KBr) 1730 and 1708 (C=O) cm^{-1}; mass spectrum, m/e 289.138 (M^+, calcd 289.131).

Anal. Calcd for $C_{16}H_{19}NO_4$ (M_r 289.335): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.34; H, 6.87; N, 4.73.

General Procedure for the Reaction of 2-(Dialkylamino)benzaldehydes (8a–c) with Malonitrile. Preparation of 11a–c. To a solution of **8a–c** (10 mmol) in 15 mL of toluene was added malonitrile (0.66 g, 10 mmol) in one portion at room temperature. After stirring for 1 h the solvent was removed under reduced pressure. The resulting solid was purified by trituration with methanol affording the pure **11a–c**.

[2-(1-Pyrrolidinyl)phenylmethylene]propanedinitrile (11a): yield, 91%; red crystals; mp 92–93 °C (methanol); ^1H NMR δ 7.99 (s, 1 H, =CH), 7.9–7.75 (m, 1 H, Ar H), 7.55–7.25 (m, 1 H, Ar H), 7.0–6.75 (m, 2 H, Ar H), 3.5–3.15 (m, 4 H, NCH_2), 2.2–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 159.4 (d, =CH), 151.3 (s, Ar C-2), 134.4, 129.7, 118.4 and 115.4 (d, Ar C), 118.9 (s, Ar C-1), 114.7 and 113.0 (s, CN), 77.3 [s, =*C*$(CN)_2$], 53.1 (t, NCH_2), 25.8 (t, CH_2); IR (KBr) 2212 (CN) cm^{-1}; mass spectrum, m/e 223.110 (M^+, calcd, 223.111).

Anal. Calcd for $C_{14}H_{13}N_3$ (M_r 223.279): C, 75.31; H, 5.87; N, 18.82. Found: C, 75.26; H, 5.93; N, 18.91.

[2-(1-Piperidinyl)phenylmethylene]propanedinitrile (11b): yield, 89%; yellow crystals; mp 123–124 °C (methanol); ^1H NMR δ 8.13 (s, 1 H, =CH), 8.2–8.0 (m, 1 H, Ar H), 7.7–7.4 (m, 1 H, Ar H), 7.3–7.0 (m, 2 H, Ar H), 3.1–2.8 (m, 4 H, NCH_2), 1.95–1.5 (m, 6 H, CH_2); ^{13}C NMR δ 157.3 (d, =CH), 155.6 (s, Ar C-2), 134.8, 129.0, 122.5 and 119.5 (d, Ar C), 124.7 (s, Ar C-1), 114.2 and 112.7 (s, CN), 80.8 [s, =*C*$(CN)_2$], 55.2 (t, NCH_2), 26.2 and 23.8 (t, CH_2); IR (KBr) 2222 (CN)cm^{-1}; mass spectrum, m/e 237.128 (M^+, calcd, 237.127).

Anal. Calcd for $C_{15}H_{15}N_3$ (M_r 237.306): C, 75.92; H, 6.37; N, 17.71. Found: C, 75.73; H, 6.36; N, 17.60.

[2-(4-Morpholinyl)phenylmethylene]propanedinitrile (11c): yield, 90%; yellow crystals; mp 133–138 °C dec (methanol); ^1H NMR δ 8.20 (s, 1 H, =CH), 8.3–8.0 (m, 1 H, Ar H), 7.8–7.5 (m, 1 H, Ar H), 7.4–7.1 (m, 2 H, Ar H), 4.0–3.75 (m, 4 H, OCH_2), 3.1–2.85 (m, 4 H, NCH_2); ^{13}C NMR δ 156.8 (d, =CH), 153.9 (s, Ar C-2), 135.1, 129.3, 123.6 and 119.5 (d, Ar C), 124.9 (s, Ar C-1), 113.9 and 112.6 (s, CN), 82.0 [s, =*C*$(CN)_2$], 66.8 (t, OCH_2), 53.9 (t, NCH_2); IR (KBr) 2225 (CN) cm^{-1}; mass spectrum, m/e 239.108 (M^+, calcd, 239.106).

Anal. Calcd for $C_{14}H_{13}N_3O$ (M_r 239.279): C, 70.28; H, 5.48; N, 17.56. Found: C, 70.08; H, 5.54; N, 17.39.

Methyl *cis*- and *trans*-2,3,9,9a-Tetrahydro-9-(methoxycarbonyl)-1*H*-pyrrolo[1,2-*a*]indole-9-acetate (12a and 12b). Reaction in Toluene. A solution of **5a** (1.16 g, 4 mmol) in 30 mL of toluene was heated at 110 °C for 24 h. After removal of the solvent under reduced pressure, the residue, dissolved in a chloroform/ethyl acetate, 1:1 mixture, was passed through a short column of silica gel. The solvents were evaporated and the resulting oil was separated by medium-pressure chromatography [silica gel, petroleum ether (bp 60–80 °C)/ethyl acetate, 2:1] to

afford the pure **12a** (54%) and **12b** (32%) as white solids.

Reaction in 1-Butanol. A solution of **5a** (0.58 g, 2 mmol) in 20 mL of 1-butanol was heated at 118 °C for 3.5 h. After removal of the solvent under reduced pressure, the remaining solid was triturated with cold diisopropyl ether to give pure **12a** in a yield of 74%.

12a: mp 107–108 °C (diisopropyl ether); ^{1}H NMR δ 7.3–7.0 (m, 2 H, Ar H), 6.7–6.45 (m, 2 H, Ar H), 4.65 (dd, 1 H, J = 5.1 and 11.1 Hz, NCH), 3.70 and 3.69 (s, 3 H, OCH_3), 3.7–3.4 (m, 1 H, NC*H*H), 3.63 and 2.72 (AB q, 2 H, J = 17.7 Hz, CH_2E), 3.25–2.9 (m, 1 H, NCH*H*), 2.1–1.1 (m, 4 H, CH_2); ^{13}C NMR δ 173.8 and 171.8 (s, C=O), 154.0 (s, C-4a), 129.6, 123.7, 119.1 and 111.1 (d, Ar C), 128.5 (s, C-8a), 72.0 (d, NCH), 54.1 [s, *C*(E)CH_2E], 52.8 and 51.9 or 51.8 (q, OCH_3), 51.9 or 51.8 (t, NCH_2), 38.9 (t, CH_2E), 26.7 and 25.6 (t, CH_2); IR (KBr) 1723 (C=O) and 1596 (C=C) cm^{-1}; mass spectrum, m/e 289.127 (M$^+$, calcd, 289.131).

Anal. Calcd for $C_{16}H_{19}NO_4$ (M_r 289.335): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.44; H, 6.57; N, 4.75.

12b: mp 89.5–91 °C (cold diisopropyl ether); ^{1}H NMR δ 7.4–7.1 (m, 2 H, Ar H), 6.9–6.5 (m, 2 H, Ar H), 3.79 (dd, 1 H, J = 5.4 and 10.25 Hz, NCH), 3.77 and 3.63 (s, 3 H, OCH_3), 3.5–3.1 (m, 2 H, NCH_2), 3.23 and 2.80 (AB q, 2 H, J = 16.2 Hz, CH_2E), 2.1–1.2 (m, 4 H, CH_2); ^{13}C NMR δ 172.2 and 170.9 (s, C=O), 153.9 (s, C-4a), 129.0, 126.8, 119.4 and 110.9 (d, Ar C), 75.1 (d, NCH), 55.1 [s, *C*(E)CH_2E], 52.0 and 51.6 (q, OCH_3), 51.6 (t, NCH_2), 44.3 (t, CH_2E), 26.6 and 25.4 (t, CH_2); IR (KBr) 1734 and 1720 (C=O) and 1601 (C=C) cm^{-1}; mass spectrum, m/e 289.127 (M$^+$, calcd, 289.131).

Anal. Calcd for $C_{16}H_{19}NO_4$ (M_r 289.335): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.52; H, 6.69; N, 4.82.

***cis*- and *trans*-2,3,9,9a-Tetrahydro-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole-9-carbonitrile (13a and 13b). Reaction in 1-Butanol.** A solution of **7a** (0.98 g, 3.6 mmol) in 20 mL of 1-butanol was heated at 118 °C for 8 days. After removal of the solvent under reduced pressure the crude reaction mixture was separated by column chromatography (silica gel, chloroform) to give **7a** (14%), **13a** (44%), and **13b** (42%). The compounds **13a–b** solidified on standing.

Reaction in Acetonitrile. A mixture of **7a** (1.57 g, 5.7 mmol) and zinc chloride (1.57 g, 11.5 mmol) in 50 mL of acetonitrile was heated at 81 °C for 21 h. After removal of the acetonitrile under reduced pressure, 50 mL of water was added to the residue. The products were isolated by extraction with chloroform (3 × 25 mL). The combined extracts were washed twice with water, dried with $MgSO_4$, and then the solvent was removed under reduced pressure. The residue was separated by column chromatography (silica gel, chloroform) to afford **7a** (8%), **13a** (47%), and **13b** (12%).

13a: mp 122–123.5 °C (diisopropyl ether); ^{1}H NMR δ 7.6–6.6 (m, 9 H, Ar H), 4.10 (dd, 1 H, J = 6.0 and 9.6 Hz, NCH), 3.52 and 3.12 (AB q, 2 H, J = 14.4 Hz, CH_2Ph), 3.5–3.1 (m, 2 H, NCH_2), 2.1–1.3 (m, 4 H, CH_2); ^{13}C NMR δ 153.1 (s, C-4a), 135.2 (s), 130.1 (d), 129.8 (d), 128.4 (d), 127.3 (d), 124.0 (d), 119.8 (d), 111.3 (d) (Ar C), 122.8 (s, CN), 74.3 (d, NCH), 50.5 (t, NCH_2), 46.4 (s, C-9), 39.1 (t, CH_2Ph), 25.3 and 25.2 (t, CH_2); IR (KBr) 2225 (CN) cm^{-1}; mass spectrum, m/e 274.147 (M$^+$, calcd, 274.147).

Anal. Calcd for $C_{19}H_{18}N_2$ (M_r 274.367): C, 83.18; H, 6.61; N, 10.21. Found: C, 83.21; H, 6.61; N, 10.18.

13b: mp 87–97 °C (diisopropyl ether); ^{1}H NMR δ 7.4–7.0 (m, 6 H, Ar H), 6.9–6.6 (m, 3 H, Ar H), 3.95–3.7 (m, 1 H, NCH), 3.5–3.1 (m, 4 H, NCH_2), 3.10 (s, 2 H, CH_2Ph), 2.1–1.3 (m, 4 H, CH_2); ^{13}C NMR δ 152.9 (s, C-4a), 134.6 (s), 130.4 (d), 129.9 (d), 128.1 (d), 127.3 (d), 124.9 (d), 119.6 (d), 111.5 (d) (Ar C), 120.1 (s, CN), 72.9 (d, NCH), 51.9 (t, NCH_2), 48.8 (s, C-9), 45.5 (t, CH_2Ph), 28.5 and 25.3 (t, CH_2); IR (KBr) 2239 (CN) cm^{-1}; mass spectrum, m/e 274.147 (M$^+$, calcd, 274.147).

Anal. Calcd for $C_{19}H_{18}N_2$ (M_r 274.367): C, 83.18; H, 6.61; N, 10.21. Found: C, 83.23; H, 6.75; N, 10.08.

6,7,8,9-Tetrahydro-10-(phenylmethyl)pyrido[1,2-*a*]indole (15b) and 6,7,8,9,9a,10-Hexahydro-10-(phenylmethyl)-pyrido[1,2-*a*]indole-10-carbonitrile (14b). A mixture of **7b** (1.10 g, 3.8 mmol) and zinc chloride (1.10 g, 8.1 mmol) in 20 mL of toluene was heated at 110 °C. After 24 h another portion of zinc chloride (0.55 g, 4.1 mmol) was added. After heating for 7 days the crude reaction mixture was washed with a saturated aqueous solution of NH_4Cl (3 × 25 mL) and subsequently dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue separated by column chromatography [silica gel, chloroform/petroleum ether (bp 60–80 °C), 1:1] to yield **15b** (26%), **7b** (5%), and **14b** (11%).

15b: oil; ^{1}H NMR δ 7.55–6.95 (m, 9 H, Ar H), 4.04 (s, 2 H, CH_2Ph), 4.1–3.9 (m, 2 H, NCH_2), 2.95–2.7 (m, 2 H, =CCH_2), 2.2–1.65 (m, 4 H, CH_2); ^{13}C NMR δ 141.6 (s), 135.8 (s), 133.5 (s), 128.1 (s + d), 125.3 (d), 120.0 (d), 119.0 (d), 117.9 (d) and 108.2 (s + d) (Ar C), 42.2 (t, NCH_2), 29.9 (t, CH_2Ph), 23.4, 22.5 and 21.1 (t, CH_2); mass spectrum, m/e 261.154 (M$^+$, calcd for $C_{19}H_{19}N$, 261.152).

14b: mp 150–157 °C dec (diisopropyl ether); ^{1}H NMR δ 7.4–6.8 (m, 6 H, Ar H), 6.7–6.2 (m, 3 H, Ar H), 3.8–3.25 (m, 2 H, NCH and NC*H*H), 3.05 and 2.83 (AB q, 2 H, J = 12.9 Hz, CH_2Ph), 2.75–2.3 (m, 1 H, NCH*H*), 2.2–1.2 (m, 6 H, CH_2); ^{13}C NMR δ 150.3 (s, C-4a), 134.7 (s), 130.7 (d), 129.2 (d), 127.7 (d), 127.0 (d), 125.7 (d), 118.3 (d) and 107.4 (d) (Ar C), 121.2 (s, CN), 73.3 (d, NCH), 47.9 (s, C-10), 46.3 (t, NCH_2), 36.8 (t, CH_2Ph), 24.5 and 24.0 (t, CH_2); IR (KBr) 2238 (CN) cm^{-1}; mass spectrum, m/e 288.162 (M$^+$, calcd, 288.163).

Anal. Calcd for $C_{20}H_{20}N_2$ (M_r 288.394): C, 83.30; H, 6.99; N, 9.71. Found: C, 83.24; H, 7.06; N, 9.74.

2,3-Dihydro-9-(phenylmethyl)-1*H*-pyrrolo[1,2-*a*]indole (15a). A mixture of **13a** (0.85 g, 3.1 mmol) and zinc chloride (3.50 g, 25.7 mmol) in 15 mL of toluene was heated at 110 °C for 24 h. To the stirred reaction mixture 15 mL of chloroform and 15 mL of water were added. After all the solid materials had dissolved the layers were separated. The water layer was extracted with chloroform (2 × 25 mL). The combined organic layers were washed twice with water, dried with $MgSO_4$, and then the solvents were removed under reduced pressure. The crude reaction mixture was passed through a short path of silica gel affording pure **15a** as an oil: yield, 61%; ^{1}H NMR δ 7.6–6.9 (m, 9 H, Ar H), 4.05 (s, 2 H, CH_2Ph), 4.1–3.9 (m, 2 H, NCH_2), 2.7–2.3 (m, 4 H, CH_2); ^{13}C NMR δ 141.8 (s), 141.6 (s), 132.5 (s), 132.4 (s), 128.6 (d), 128.1 (d), 125.6 (d), 120.0 (d), 118.5 (d), 109.1 (d), 104.6 (s) (Ar C), 43.4 (t, NCH_2), 31.0 (t, CH_2Ph), 27.7 and 23.2 (t, CH_2); mass spectrum, m/e 247.134 (M$^+$, calcd for $C_{18}H_{17}N$, 247.136).

General Procedure for the Ring Closure of 10 and 11a–c. Preparation of 16a–b, 17, 18. A solution of **10** or **11a–c** (1.0 g) in 15 mL of 1-butanol was refluxed for 22, 2, 2, and 35 h, respectively. Upon cooling the compounds **16b**, **17**, and **18** crystallized spontaneously from the crude reaction mixture. In the case of **16a** the crystallization occurred after removal of most of the solvent under reduced pressure. Filtration and washing with cold methanol (2 × 10 mL) afforded the pure **16a–b**, **17**, and **18** as white crystals.

Dimethyl 1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarboxylate (16a): yield, 67%; mp 94–95 °C (methanol); ^{1}H NMR δ 7.2–6.9 (m, 2 H, Ar H), 6.8–6.3 (m, 2 H, Ar H), 3.78 and 3.55 (s, 3 H, OCH_3), 3.85–3.65 (m, 1 H, NCH), 3.4–3.1 (m, 4 H, NCH_2 and ArCH_2), 2.5–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 171.2 and 168.8 (s, C=O), 143.6 (s, C-9a), 128.3, 127.4, 115.8 and 110.8 (d, Ar C), 118.5 (s, C-5a), 62.0 (d, NCH), 53.2 [s, *C*(E)$_2$], 52.6 and 52.0 (q, OCH_3), 47.4 (t, NCH_2), 36.9 (t, ArCH_2), 27.9 and 23.5 (t, CH_2); IR (KBr) 1723 (C=O) cm^{-1}; mass spectrum, m/e 289.137 (M$^+$, calcd, 289.131).

Anal. Calcd for $C_{14}H_{19}NO_4$ (M_r 289.335): C, 66.42; H, 6.62; N, 4.84. Found: C, 66.49; H, 6.62; N, 4.77.

1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (16b): yield, 82%; mp 127–135 °C dec (diisopropyl ether); ^{1}H NMR δ 7.3–6.95 (m, 2 H, Ar H), 6.85–6.5 (m, 2 H, Ar H), 3.79 (dd, 1 H, J = 5.85 and 7.8 Hz, NCH), 3.6–3.2 (m, 2 H, NCH_2), 3.48 (s, 2 H, ArCH_2), 2.65–1.8 (m, 4 H, CH_2); ^{13}C NMR δ 141.7 (s, C-10a), 129.1, 128.8, 117.4 and 112.0 (d, Ar C), 113.4 (s, C-6a), 114.9 and 113.0 (s, CN), 62.8 (d, NCH), 47.8 (t, NCH_2), 38.1 (t, ArCH_2), 33.9 [s, *C*(CN)$_2$], 29.9 and 22.8 (t, CH_2); IR (KBr) 2246 (CN) cm^{-1}; mass spectrum, m/e 223.110 (M$^+$, calcd, 223.111).

Anal. Calcd for $C_{14}H_{13}N_3$ (M_r 223.279): C, 75.31; H, 5.87; N, 18.82. Found: C, 75.29; H, 5.84; N, 18.88.

2,3,4,4a,5,6-Hexahydro-1*H*-benzo[*c*]quinolizine-5,5-dicarbonitrile (17): yield, 78%; mp 127–139 °C dec (methanol); ^{1}H NMR δ 7.4–6.7 (m, 4 H, Ar H), 4.2–3.9 (m, 1 H, NCH), 3.47 (s, 2 H, ArCH_2), 3.5–3.2 (m, 1 H, NC*H*H), 3.0–2.55 (m, 1 H, NCH*H*), 2.45–1.3 (m, 6 H, CH_2); ^{13}C NMR δ 144.0 (s, C-10a), 129.2, 128.9, 119.2 and 113.8 (d, Ar C), 115.5 (s, C-6a), 114.7 and 113.7 (s, CN), 59.8 (d, NCH), 48.1 (t, NCH_2), 37.1 [s, *C*(CN)$_2$], 36.7 (t,

$ArCH_2$), 28.9, 24.3 and 23.1 (t, CH_2); IR (KBr) 2245 (CN) cm^{-1}; mass spectrum, m/e 237.128 (M^+, calcd, 237.127).

Anal. Calcd for $C_{15}H_{15}N_3$ (M_r 237.306): C, 75.92; H, 6.37; N, 17.71. Found: C, 75.93; H, 6.55; N, 17.75.

1,2,4,4a,5,6-Hexahydro[1,4]oxazino[4,3-*a*]quinoline-5,5-dicarbonitrile (18): yield, 84%; mp 110–160 °C dec (methanol); ^1H NMR δ 7.4–6.75 (m, 4 H, Ar H), 4.5–2.75 (m, 9 H, other hydrogen atoms); ^{13}C NMR δ 143.5 (s, C-10a), 129.3, 129.0, 120.3 and 113.1 (d, Ar C), 115.4 (s, C-6a), 113.5 and 112.8 (s, CN), 68.1 and 66.1 (t, OCH_2), 56.8 (d, NCH), 45.7 (t, NCH_2), 37.2 (t, $ArCH_2$), 33.1 [s, $C(CN)_2$]; IR (KBr) 2248 (CN) cm^{-1}; mass spectrum, m/e 239.109 (M^+, calcd, 239.106).

Anal. Calcd for $C_{14}H_{13}N_3O$ (M_r 239.279): C, 70.28; H, 5.48; N, 17.56. Found: C, 70.17; H, 5.53; N, 17.46.

Crystallographic Data and X-ray Structure Analysis of 13a. Crystals of **13a** are triclinic, space group $P\bar{1}$: a = 10.91 (1) b = 9.570 (3), c = 8.758 (8) Å; α = 65.15 (1), β = 66.94 (3), γ = 71.24 (1)°; Z = 2; d_c = 1.21 g cm^{-3}. Intensities were measured by using Mo Kα radiation [Philips PW1100 diffractometer, graphite monochromator, $\theta - 2\theta$ scan mode, $3 < \theta < 25°$, scan speed 0.025° s^{-1}, scan width deg 1.7 + 0.6 tan θ]. The total number of independent reflexions measured was 2384. The structure was solved by direct methods[31] and refined by full-matrix least-squares[32] to a final R-factor of 4.8%. In the refinements 1934 reflections with intensities greater than the standard deviation from counting statistics were used. Hydrogen atoms were found from difference Fourier syntheses. In the last cycles 263 parameters were refined (scale factor, extinction parameter, positional parameters of all atoms, thermal parameters of all atoms: anisotropic for non-hydrogen atoms, isotropic for hydrogen atoms). The drawing of the structure was made by ORTEP.[33]

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Registry No. **4a**, 87698-81-5; **4b**, 82212-00-8; **4c**, 87698-82-6; (*Z*)-**5a**, 83466-98-2; (*Z*)-**5b**, 87698-83-7; (*Z*)-**5c**, 87698-84-8; **6a**, 87698-85-9; **6b**, 40377-01-3; **6c**, 87698-86-0; (*Z*)-**7a**, 87698-87-1; (*E*)-**7a**, 87698-88-2; (*Z*)-**7b**, 87698-89-3; (*E*)-**7b**, 87698-90-6; (*Z*)-**7c**, 87698-91-7; (*E*)-**7c**, 87698-92-8; **8a**, 58028-74-3; **8b**, 34595-26-1; **8c**, 58028-76-5; **9**, 87698-93-9; **10**, 87698-94-0; **11a**, 87698-95-1; **11b**, 87698-96-2; **11c**, 87698-97-3; **12a**, 87698-98-4; **12b**, 87698-99-5; **13a**, 87699-00-1; **13b**, 87711-10-2; **14b**, 87699-01-2; **15a**, 87699-02-3; **15b**, 87699-03-4; **16a**, 87699-04-5; **16b**, 87699-05-6; **17**, 87699-06-7; 18, 87699-07-8; 2-bromoaniline, 615-36-1; 2-aminobenzeneacetonitrile, 2973-50-4; 1,4-dibromobutane, 110-52-1; 1,5-dibromopentane, 111-24-0; 1,1'-oxybis(2-bromoethane), 5414-19-7; benzaldehyde, 100-52-7; triethyl phosphonoacetate, 867-13-0; dimethyl malonate, 108-59-8; malononitrile, 109-77-3; DMAD, 762-42-5.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

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Regioselectivity Associated with the 1,3-Dipolar Cycloaddition of Nitrones with Electron-Deficient Dipolarophiles

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A study of the cycloaddition behavior of a series of electron-deficient dipolarophiles with *C*-aryl-*N*-alkylnitrones has been carried out. The 1,3-dipolar cycloaddition proceeds in high yield to produce isoxazolidines. This [3 + 2] cycloaddition embodies a high degree of both regiochemical and stereochemical control and provides an efficient entry into such heterocyclic systems. The reactions follow frontier orbital predictions. Most dipolarophiles undergo cycloaddition to give 5-substituted isoxazolidines. The orientation has been explained in terms of maximum orbital overlap of the nitrone LUMO–dipolarophile HOMO. As the electron affinity of the dipolarophile increases, an increasing tendency toward formation of the 4-substituted isoxazolidine is encountered. In certain cases diastereomeric isoxazolidines were formed via different two-plane orientation complexes. The ratio of the diastereomers reflects the free energy difference of the two transition states. This difference comes from repulsive interactions caused by steric hindrance and attractive van der Waal forces associated with maximum π overlap of the substituent groups. The transition state which dominates in a particular case will depend on the nature of the groups attached to the N atom of the nitrone and to the dipolarophile π bond.

The 1,3-dipolar cycloaddition reaction is one of the most useful reactions for the synthesis of heterocyclic compounds.[1,2] It provides the chemist one of his best tools for constructing five-membered rings and has a nearly singular capability of establishing large numbers of stereochemical centers in one synthetic step. Nitrones represent a long-known and thoroughly investigated class of 1,3-dipoles.[3-7] The cycloaddition of nitrones with alkenes produces isoxazolidines in high yield.[8,9] The presence of a nitrogen atom within the isoxazolidine ring has made this heterocyclic moiety especially attractive for the synthesis

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