Reaction of $N^1,N^2$-Diarylamidines with (2,3-Diphenylcyclopropen-1-ylidene)propanedinitrile: Synthesis of [2-Arylamino-4(1H)-pyridinylidene]-propanedinitriles

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Abstract: A series of new [1-aryl-2-arylamino-5,6-diphenyl-4(1H)-pyridinylidene]propanedinitriles 3a–e has been synthesized by the reaction of $N^1,N^2$-diarylamidines 1a–e with (2,3-diphenylcyclopropen-1-ylidene)propanedinitrile (2). Structures of 3a–e have been assigned on the basis of NMR spectra and NOE experiments.

Key words: pyridines, regioselectivity, ring expansion, cycloaddition, dicyanomethylene compounds

The design and synthesis of 1,4-dihydropyridines has attracted much attention within the past thirty years due to the calcium antagonist effect they display. It was reported that 1,4-dihydropyridines exhibit pharmacological action as drugs for the treatment of cardiovascular diseases such as angina, hypertension or arrhythmia. Sugiyama et al. have reported the synthesis of (2,6-dimethoxycarbonyl)-2-diarylamidines with four or five substituents from the reaction of 4-chloropyridine-2,6-dicarboxylate and malononitrile. Similarly, [2,5-di(ethoxycarbonyl)-1-phenyl-4(1H)-pyridylidene]propanedinitrile was obtained starting from the corresponding 1-phenyl-4(1H)-pyridone. In 1990 Gewald reported the preparation of the (1H)-pyridin-4-ylidenepropanedinitrile B from cyanoacetoamide, sulfur and methyl iodide in the presence of sodium ethoxide. However, tetra- or pentasubstituted 4(1H)-pyridin-4-ylidenepropanedinitriles have so far not been reported.

This paper deals with cycloadditions of amidines to the triafulvene 2. A brief look on the cycloadditions of imines to 2 reveals that these take place in a variety of ways. Earlier, Eicher and his co-workers have reported the formation of 2-dicyanomethylene-1,2,3,4-tetrahydropyridin(2,1-α)isoquinolines from the reaction of 2 with 1-alkyl-3,4-dihydroisoquinoline via a formal [3+3] cycloaddition reaction of their enamine tautomers on C-1/C-2 of the three-membered ring of the ylidene 2, whereby the isoquinoline N-atom was linked to C-1 and the enamine β-C-atom to C-2 of the ylidene 2. In contrast, 2 reacted with the enamine tautomers of 2-aryl-1-pyrrolines via a formal [$\pi^2+\pi^n$] addition of the C=N double bond across the C-2/C-3 double bond of 2, finally giving 4-dicyanomethylene-5,6-tetra-methylene-1-azabicyclo[4.3.0]non-2-ene. When 1-morpholinobuta-1,3-diene or 1-trimethylsilyloxybuta-1,3-diene was reacted with 2, 1-dicyanomethyleneacycloheptadienes were formed through a formal [4+2] cycloaddition reaction of the diene structure to C-2/C-3 of the ylidene 2 followed by ring expansion, but when 2 reacted with ynamines, 5-dicyanomethylene-2-aminocyclopentadiene derivatives were formed via a formal [3+2] cycloaddition reaction.

In this paper we describe the synthesis of novel 1,4-dihydropyridines 3a–e with four or five substituents from the reaction of $N^1,N^2$-diarylamidines 1a–e and (2,3-diphenylcyclopropen-1-ylidene)propanedinitrile (2) by refluxing equimolar amounts of the reactants in $N,N$-dimethylformamide as solvent. Compounds 3a–e were obtained as crystalline solids in 52–70% yields (Scheme 1).

Compounds 3a–e show IR absorptions for NH groups at 3224–3432 cm$^{-1}$ and two bands corresponding to the two C=N groups, the first at 2184–2187 cm$^{-1}$, the second at 2136–2167 cm$^{-1}$. The $^1$H NMR spectra of compounds 3a–e showed the NH proton signals at $\delta = 5.36–5.88$ ppm. The singlets for 3-H of 3a–c appear at $\delta = 6.00–6.21$ ppm. In the $^13$C NMR spectra of 3a–e signals at $\delta = 41.3–43.4$ ppm were assigned to the methylenic carbon atoms [(C(CN))$_2$] in accord with the chemical shifts reported for dicyanomethylene carbons in the related compound B (see above, $\delta = 45.3$ ppm in DMSO-$d_6$) and other similar push-pull olefins. By consulting the DEPT 135/90 spectra (see above) the quaternary carbon signals at $\delta = 119.2–119.4$ (for 3a–c) and 118.5 ppm (3d) as well as at 118.9

![Figure 1](image_url) Structures of 1,4-dihydropyridines A and B

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The 1,4-dihydropyridines 3 very likely takes place (similar to the rationalization given by Eicher\(^6\)\(^–\)\(^8\) for the reaction of 2 with enamines but with opposite directionality) as depicted in Scheme 2 (for explanation of Ar and R, see Scheme 1) through a formal [3+3] cycloaddition reaction between the ketene aminal tautomer of amidine 1 and ylidene 2 (conceivably via ring-opened species 7) leading to intermediates 4\(\text{a–e}\) and further to 5\(\text{a–e}\). The latter undergo a thermal dehydrogenation to afford the title compounds 3\(\text{a–e}\). The relevance of N,C-tautomerism of amides in their reactions with electrophilic carbon atoms has been firmly established.\(^1\)\(^3\)

In conclusion, we have described a synthesis of new polysubstituted 1,4-dihydro-2-aminopyridinines in one step from amides 1\(\text{a–e}\) which exert their ambident nature and react enamine-like with the ylidene 2 via a formal [3+3] cycloaddition reaction, followed by thermal dehydrogenation under the reaction conditions affording the title compounds. The novelty in this reaction is that amides react like enamines with 2 but the direction of addition is reversed, i.e. the imino nitrogen atom of 1\(\text{a–e}\) is linked to C-2 of 2 but not to C-1 as it was reported by Eicher\(^6\)\(^–\)\(^8\) for the additions of certain imines to 2.\(^5\)\(^\text{b}\)\(^–\)\(^e\)

The uncorrected melting points were determined on a Reichert Thermovar hot stage microscope. Elemental analyses were obtained on a Carlo Erba 1106 CHN analyzer, while the IR spectra were recorded from KBr pellets on a Perkin Elmer 983 spectrophotometer. The 300 MHz \(^1\)H and 75 MHz \(^{13}\)C NMR spectra were observed on a Bruker Avance 300 instrument (300 MHz for \(^1\)H) using toluene–EtOAc (10:1) as developing solvent. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light and extracted out with acetone or EtOAc.

Formation of the 1,4-dihydropyridines 3 very likely takes place (similar to the rationalization given by Eicher\(^6\)\(^–\)\(^8\) for the reaction of 2 with enamines but with opposite directionality) as depicted in Scheme 2 (for explanation of Ar and R, see Scheme 1) through a formal [3+3] cycloaddition reaction between the ketene aminal tautomer of amidine 1 and ylidene 2 (conceivably via ring-opened species 7) leading to intermediates 4\(\text{a–e}\) and further to 5\(\text{a–e}\). The latter undergo a thermal dehydrogenation to afford the title compounds 3\(\text{a–e}\). The relevance of N,C-tautomerism of amides in their reactions with electrophilic carbon atoms has been firmly established.\(^1\)\(^3\)

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Synthesis of [2-Arylamino-4(1H)-pyridinylidene]propanedinitriles

1H NMR (CDCl₃): δ = 2.32 (s, 3 H, CH₃), 2.51 (s, 3 H, CH₃), 5.84 (s, 1 H, NH), 6.13 (s, 1 H, 3-H), 6.90–7.25 (m, 14 H, ArH), 7.45 (d, 3 J = 8.4 Hz, 2 H, ArH), 7.54 (d, 3 J = 8.4 Hz, 2 H, ArH).

13C NMR (CDCl₃): δ = 21.0 (CH₃) 21.6 (CH₃), 41.3 [C(CN)₂], 99.0 (C-3), 119.3 (2 CN), 124.4 (C-5), 154.6 (C-2), 154.7 (C-6); 125.7, 127.8 (2 close lying signals), 127.9, 128.3, 128.4, 128.8, 130.7, 131.8, 132.4 (all aryl CH); 132.8, 133.6, 135.7, 137.8, 139.0, 142.7 (other quart. C).

MS (70 eV): m/z (%) = 490 (M⁺, 100), 462 (4), 413 (8), 335 (17), 245 (6), 191 (12), 106 (13), 91 (12).


1-[(4-Methoxyphenyl)-2-(4-methoxyphenylamino)-5,6-diphenyl-4(1H)-pyridinylidene]propanedinitrile (3b)

IR (KBr): 3423 (NH), 2184, 2136 cm⁻¹ (C≡N).

1H NMR (CDCl₃): δ = 3.87 (s, 3 H, OCH₃), 3.92 (s, 3 H, OCH₃), 5.82 (s, 1 H, NH), 6.00 (s, 1 H, 3-H), 6.88–7.48 (m, 18 H, ArH).

13C NMR (CDCl₃): δ = 55.6 (OCH₃) 55.8 (OCH₃), 41.9 [C(CN)₂], 98.7 (C-3), 119.2 (2 CN), 122.0 (C-5); 115.3, 116.9, 127.7, 127.8, 128.3, 128.4, 130.4, 131.9, 132.4 (all aryl CH); 132.7, 133.6, 135.7, 139.1, 149.8, 150.9, 154.6, 154.7, 155.8 (quart. C).

MS (70 eV): m/z (%) = 522 (M⁺, 100), 457 (11), 435 (3), 413 (3), 272 (4), 91 (3), 57 (10), 44 (16).


1-[(3-Methyl-1-(4-methylphenyl)-2-(4-methylphenylamino)-5,6-diphenyl-4(1H)-pyridinylidene]propanedinitrile (3d)

Orange crystals; yield: 0.13 g (52%); mp 304–305 °C (cyclohexane).

IR (KBr): 3262 (NH), 2188, 2151 cm⁻¹ (C≡N).

1H NMR (CDCl₃): δ = 1.28 (s, 3 H, 3-CH₃), 2.28 (s, 3 H, CH₃), 2.46 (s, 3 H, CH₃), 5.36 (s, 1 H, NH), 6.59–7.39 (m, 18 H, ArH).

13C NMR (CDCl₃): δ = 16.9 (3-CH₃), 20.7 (CH₃), 21.5 (CH₃), 43.4 [C(CN)₂], 115.7 (C-3) 118.5 (2 CN); 118.2, 127.5, 128.0 (2 C), 155.5 (quart. C).

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Scheme 2
128.1 (2 C), 128.2, 130.3, 131.4, 131.8 (all aryl CH); 129.3, 133.0, 134.7, 135.7, 137.4, 138.5, 142.2, 144.3, 155.02, 156.7 (quart. C).

MS (70 eV); \( m/z \) (%): 504 (M+, 100), 467 (S), 349 (9), 334 (9), 106 (12), 91 (11), 77 (5).


[3-Methyl-1-(4-methoxyphenyl)-2-(4-methoxyphenylamino)-5,6-diphenyl-4(1\(H\))-pyridinylidene]propanedinitrile (3e)

Orange crystals; yield: 0.15 g (56%); mp 265–266 \( ^\circ \)C (EtOAc).

IR (KBr): 3224 (NH), 2187, 2167 cm\(^{-1}\) (C≡N).

\(^1\)H NMR (CDCl\(_3\)): \( \delta = 1.52 \) (s, 3 H, 3-CH\(_3\)), 3.76 (s, 3 H, OCH\(_3\)), 3.87 (s, 3 H, OCH\(_3\)), 5.44 (s, 1 H, NH), 6.71 (d, \( J = 9.0 \) Hz, 2H, Ar), 6.81 (d, \( J = 9.0 \) Hz, 2H, Ar), 7.04–7.26 (m, 10 H, ArH), 6.89 (d, \( J = 8.5 \) Hz, 2H, ArH), 7.33 (d, \( J = 8.5 \) Hz, 2H, ArH).

\(^13\)C NMR (CDCl\(_3\)): \( \delta = 16.9 \) (3-CH\(_3\)), 42.7 [C(CN)\(_2\)], 55.6 (OCH\(_3\)), 14.5 (C-3), 118.9 (2 CN); 114.9, 116.4, 120.8, 127.4, 127.9, 128.0, 128.1, 128.2, 129.7, 131.5 (all aryl CH); 128.4, 129.6, 134.1, 135.8, 137.5, 145.7, 155.0, 156.2, 156.5, 161.8 (quart. C).

MS (70 eV); \( m/z \) (%): 536 (M+, 100), 522(3), 427 (4), 403 (5), 365 (4), 205 (7), 122 (8), 77 (3), 44 (8).

Anal. Calcd for C\(_{35}\)H\(_{28}\)N\(_4\)O\(_2\) (536.6): C, 78.34; H, 5.26; N, 10.44. Found C, 78.20; H, 5.18; N, 10.23.

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