

Note

α -Oxonitrile as a potential acylating agent

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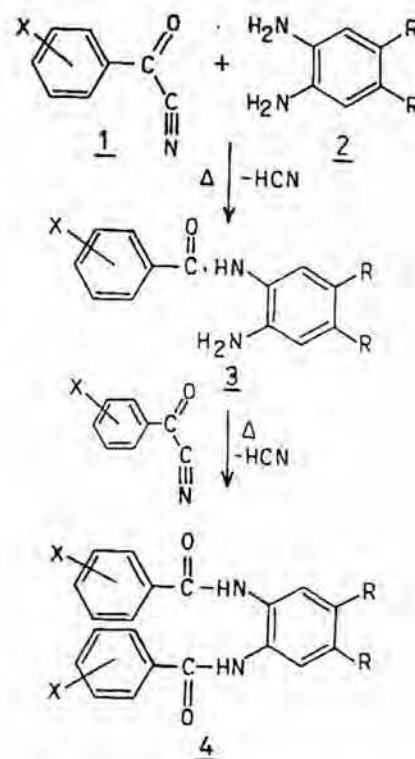
The synthetic potential of α -oxonitrile used as *N*-acylating agent under almost neutral conditions has been explored. Unreported five *N,N'*-dibenzoyl derivatives **4a-d, g** and two *N*-benzoyl derivatives **3a-c** from 4,5-dimethyl-1,2-phenylenediamine **2** and 1,2-phenylenediamine **2** have been synthesized. Their spectral data as well as antibacterial screening of *N,N'*-4,5-dimethyl-1,2-phenylenediamines are reported.

In continuation of our earlier work¹⁻⁵ on the utilization of α -oxonitriles **1** in heterocyclic synthesis and our interest in the quinoxaline chemistry due to its herbicidal⁶ and anticancer activity⁷, we attempted to synthesize quinoxalines by the action of α -oxonitrile on 4,5-dimethyl-1,2-phenylenediamine. But we obtained *N,N'*-diaroyl-4,5-dimethyl-1,2-phenylenediamine. It has been documented that aryl cyanide **1** acts as a good and selective acylating agent⁸⁻¹⁰, better than benzoyl chloride¹¹. Literature survey reveals that no work is cited on acylation of 4,5-dimethyl-1,2-phenylenediamine and 1,2-phenylenediamine with α -oxonitrile. Therefore, we became interested to synthesize a series of 4,5-dimethyl-*N,N'*-diaroyl-1,2-phenylenediamine and *N,N'*-diaroyl-1,2-phenylenediamine, and to study their pathogenic antibacterial properties.

The synthesis was carried out by heating a homogeneous mixture of 4,5-dimethyl-1,2-phenylenediamine **2** with aryl cyanide **1** at 60-130°C to give the corresponding *N,N'*-diaroyl-1,2-phenylenediamine **4**. The synthetic approach to these compounds is outlined in Scheme I.

Results and Discussion

The electrophilicity of both carbonyl and cyano functions in α -oxonitriles is enhanced by the proximity of each other. Weakly nucleophilic NH_2 group of **2** preferentially attacks at the carbonyl carbon of **1** forming a tetrahedral intermediate. From



Compd	3a	3b	3c	3d	4a	4b	4c	4d	4e	4f	4g	4h
R=	CH ₃	CH ₃	CH ₃	H	CH ₃	CH ₃	CH ₃	CH ₃	H	H	H	H
X=	H	4-CH ₃	4-Cl	H	H	3-CH ₃	3-CH ₃	4-NO ₂	H	4-CH ₃	4-Cl	4-SO ₂

Scheme I

which the CN^- ion is lost as a pseudohalogen whereby the formation of *N*-aroyl-1,2-phenylenediamine **3** occurs. The second molecule of aryl cyanide is similarly attacked by the NH_2 of monoaroyl derivative **3** to give *N,N'*-diaroyl-1,2-phenylenediamine **4**.

The acylation of aromatic diamines is simply carried out by heating the reagents together for 1-6 hr in the absence of any solvent. The same products were obtained when reaction was carried out in dry ether as solvent. The reaction, however, fails with 4-anisoyl cyanide.

A mixture of benzoyl cyanide and 4,5-dimethyl-1,2-phenylenediamine reacted at room temperature to give the *N*-monobenzoyl and *N,N'*-dibenzoyl products. The IR, ¹H NMR, mass spectra and micro-analytical data of the *N*-monobenzoyl **3a-d** and *N,N'*-dibenzoyl derivatives **4a-h** are in accordance with the proposed structures. For example, the IR spectra of

the compounds in nujol revealed the absence of $C\equiv N$ group and showed absorption bands at $3500\text{--}3240\text{ cm}^{-1}$ for NH stretching, at $1660\text{--}1640\text{ cm}^{-1}$ for $C=O$ stretching, and at $1610\text{--}1580\text{ cm}^{-1}$ for the aromatic ring. The ^1H NMR spectra showed the presence of two CH_3 groups, aromatic protons and two NH protons for N,N' -dibenzoyl derivatives **4**. The molecular ion peak of 4,5-dimethyl- N,N' -dibenzoyl-1,2-phenylenediamine **4a** was observed at m/z 344(M^+). Other peaks at m/z 239 ($M^+ - \text{C}_6\text{H}_5\text{CO}$), 222 ($M^+ - \text{NHCOC}_6\text{H}_5 - 2\text{H}^+$) and a base peak at 105 ($\text{C}_6\text{H}_5\text{CO}$) were located. The molecular ion peak of 4,5-dimethyl- N -benzoyl-1,2-phenylenediamine **3a** is observed at m/z 240(M^+). Other peaks are at m/z 135($M^+ - \text{C}_6\text{H}_5\text{CO}$) with a base peak at 105 ($\text{C}_6\text{H}_5\text{CO}$).

Antimicrobial susceptibility of the synthesized compounds **3c**, **4a-d** were evaluated by the disc-diffusion method modified by Bauer *et al.*¹² at 1000 ppm concentration against seventeen different strains of pathogenic microorganisms namely, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, *Proteus vulgaris*, *Providencia rettgeri*, *Salmonella typhi*, *Salmonella typhimurium*, *Strigella dysenteriae*, *Vibrio cholerae* 01, *Vibrio cholerae* non 01, *Vibrio parahaemolyticus*, *Aeromonas hydrophila*, *Plesimonas shigelloids*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Edwardsiella tarda*. The antimicrobial screening results indicate that the compound **3c** is active (zone of inhibition, 11-15 mm) against *C. freundii* and *V. parahaemolyticus*; **4a** is active against *P. aeruginosa*, *S. typhi*, *V. cholerae* 01 and *V. cholerae* non 01; **4c** is active against *C. freundii* and *P. rettgeri*, and **4d** against bacteria *V. cholerae* non 01 only. Compound **4b** is inactive (zoine of inhibition 0-2.5 mm) against all the tested bacteria.

Experimental Section

All melting points ($^{\circ}\text{C}$) were determined in open capillaries with a Gallenkamp apparatus and are uncorrected. The progress of the reaction and the purity of the compounds were routinely checked by TLC using silica gel G (E. Merck) plates. The IR spectra were recorded on a Jasco FT-IR 5300 spectrophotometer, ^1H NMR spectra on a Jeol FX-90Q Fourier transform spectrometer (90 MHz instrument) at the probe temperature 27°C with TMS as an internal standard and mass spectra on a Hewlett-Packard LCMX 5989-In spectrophotometer. Perkin-

Elmer CHN Analyzer 240C was used for elementary analysis.

α -Oxonitriles **1** were prepared by known methods¹³. 4,5-Dimethyl-1,2-phenylenediamine and 1,2-phenylenediamine were Aldrich products.

4, 5-Dimethyl- N, N' -dibenzoyl-1, 2-phenylene-diamine 4a. Benzoyl cyanide (**1**, 4.45 g, 34 mmoles) and 3,4-dimethyl-1,2-phenylenediamine (**2**, 2.3 g, 17 mmoles) were homogeneously mixed at room temperature. A vigorous exothermic reaction took place. Reaction mixture was then heated at 50°C for 30 min to ensure completion of the reaction. The solid mass was triturated with cold water, filtered and washed with a little benzene. Recrystallization of the solid with benzene : ethanol (3:1) mixture gave colourless shining crystals of **4a**, yield 3.7 g (55%), mp 255°C . Anal. calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$: C, 76.7; H, 5.8; N, 8.1. Found: C, 76.9; H, 5.7; N, 7.9%. IR (Nujol): $3420, 3240, 1650, 1610, 1600, 1580\text{ cm}^{-1}$; ^1H NMR (CDCl_3): δ 9.66 (2H, s, NH), 8.44-7.11 (12H, m, ArH), 1.57 (6H, s, CH_3). MS: m/z 345 ($M^+ + 1$), 344 (M^+), 327, 239, 222, 207, 136, 105, 94.

The mother liquor obtained above was concentrated and the product was recrystallized with benzene: ethanol mixture (3:1) to give needle shaped colourless crystals of 4,5-dimethyl- N -benzoyl-1,2-phenylenediamine **3a**, yield 1.7 g (25%), mp 160°C . Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$: C, 75.0; H, 6.6; N, 11.7. Found: C, 75.1; H, 6.4; N, 11.7%. IR (Nujol): $3450, 3300, 1660, 1600, 1580\text{ cm}^{-1}$. ^1H NMR (CDCl_3): δ 9.22 (1H, brs, NH), 8.22-6.57 (7H, m, ArH), 3.22 (2H, br, NH_2), 2.22 (6H, s, CH_3); MS: m/z 241 ($M^+ + 1$), 240 (M^+), 223, 207, 135, 118, 105, 93.

Other N,N' -dibenzoyl **4b-h** and N -monobenzoyl **3b-c** derivatives were prepared as described above. Their physical and spectral data are given below:

4b: Yield 4.3 g (60%), mp $288\text{--}90^{\circ}\text{C}$. Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2$: C, 77.4; H, 6.4; N, 7.5. Found: C, 77.2; H, 6.5; N, 7.3%. IR (Nujol): $3420\text{--}3220, 1700, 1610, 1600\text{ cm}^{-1}$; ^1H NMR ($\text{DMSO}-d_6$): δ 8.39 (2H, d, NH), 8.00-7.22 (10H, m, ArH), 2.40 (12H, s, CH_3); MS: m/z 373 ($M^+ + 1$), 372 (M^+), 355, 253, 236, 105

3b: Yield 1.7 g (23%), mp 182°C . Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$: C, 75.5; H, 7.1; N, 11.0. Found: C, 75.6; H, 7.6; N, 11.0%. IR (Nujol): $3480\text{--}3360, 1680, 1600, 1580\text{ cm}^{-1}$; ^1H NMR ($\text{DMSO}-d_6$): δ 9.66 (1H, br, NH); δ 7.66-6.57 (6H, m, ArH), 4.11 (2H, brs, NH_2), 2.04 (9H, s, CH_3); MS: m/z 254 ($M^+ + 1$), 254 (M^+), 237, 135, 105

4c: Light brown crystals from benzene. Yield 4.0 g (55%), mp 245°C (dec). Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.4; H, 6.4; N, 7.5. Found: C, 77.7; H, 6.5; N, 7.8%. IR (Nujol): 3400, 1680, 1605, 1580 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 7.66-6.66 (10H, m, ArH), 6.31 (2H, brs, NH), 2.22 (12H, s, CH_3).

3c: When a homogeneous mixture of 4-chlorobenzoyl cyanide and 4,5-dimethyl-1,2-phenylenediamine in 2:1 molar ratio was heated for 6 hr only monoacylated derivative **3c** was obtained, yield 4.7 g (60%), mp 137°C (benzene). Anal. Calcd for $C_{15}H_{15}N_2ClO$: C, 65.7; H, 1.8; N, 10.2%. Found: C, 65.6; H, 1.5; N, 10.4. IR (Nujol): 3400, 3350, 1660, 1580 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 8.22-6.22 (7H, m, 6 ArH & one NH), 5.78-4.22 (2H, brs, NH_2), 2.00 (6H, s, CH_3).

4d: Yield 5.5 g (65%), mp 265°C (EtOH). Anal. Calcd for $C_{22}H_{18}N_4O_6$: C, 60.8; H, 4.1; N, 13.0. Found: C, 61.0; H, 4.3; N, 12.73%. IR (Nujol): 3600-3330, 1700, 1620, 1560 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 8.88-8.00 (10H, m, ArH), 7.44 (2H, s, NH), 2.35 (6H, s, CH_3).

4e: Yield 2.5 g (40%), mp 298-99°C (Lit¹⁴, mp 301°C). IR (Nujol): 3260, 3180, 1660, 1600, 1580 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 10.25 (2H, s, NH), 8.44-6.90 (14H, m, ArH).

3d: Obtained by concentration of the mother liquor of **4e**, yield 2.5 g (40%), mp 140-41°C (Lit¹⁴, mp 140°C). IR (Nujol): 3400, 3270, 1680, 1600, 1575 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 8.55-7.00 (10H, m, 9 ArH and NH), 3.81 (2H, s, NH_2).

4f: Yield 2.7 g (43%), mp 230°C (DMF) (Lit¹⁴, mp 228°C). IR (Nujol): 3270, 3180, 1670, 1600, 1570 cm^{-1} ; ^1H NMR (DMSO- d_6): δ 10.24, (2H, s, NH), 8.19-7.36 (12H, m, ArH), 2.53 (6H, s, CH_3).

4g: Yield 4.0 g (54%), mp 253-54°C (DMF). Anal. Calcd for $C_{20}H_{24}Cl_2N_2O_2$: C, 62.33; H, 3.63; N, 7.27. Found: C, 62.4; H, 3.6; N, 7.2%. IR (Nujol): 3450, 3275, 3180, 1660, 1600, 1540 cm^{-1} ; ^1H NMR

(DMSO- d_6): δ 10.51 (2H, s, NH), 9.02-7.20 (12H, m, ArH).

4h: Yield 3.7 g (48%), mp 260-61°C (DMF) (Lit¹⁴, mp 267°C). IR (Nujol): 3275, 3175, 1660, 1610, 1530 cm^{-1} ; ^1H NMR (DMSO- d_6): 9.78-8.31 (12H, m, ArH), 7.49 (2H, brs, NH).

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