Studies with Functionally Substituted Heteroaromatics: The Chemistry of *N*-Phenylhydrazonylalkylpyridinium Salts and of Phenylhydrazonylalkylbenzoazoles

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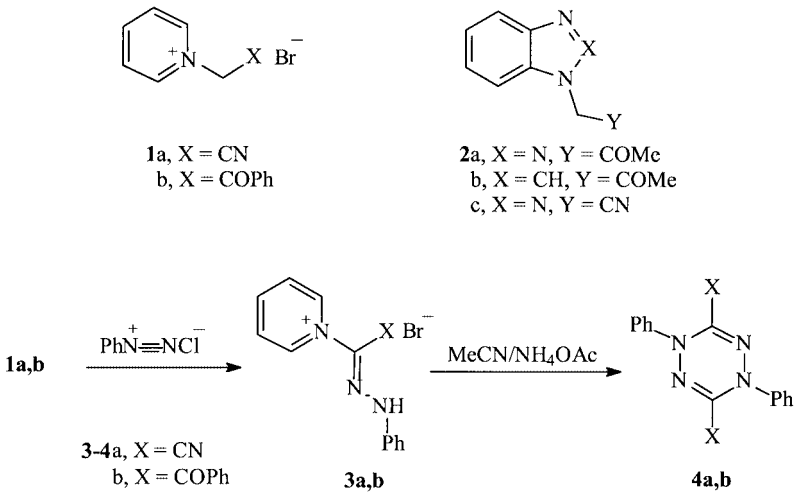
Abstract: 2-Pyrid-1-yliniumacetonitrile bromide **1a** and 2-pyrid-1-ylinium-1-phenylethanone bromide **1b** coupled with benzenediazonium chloride to yield the corresponding phenylhydrazones **3a, b**. Similarly, compounds **2a**–**c** also coupled with aryldiazonium chloride, yielding the arylhydrazones **10a**–**b,** which were used as precursors for the synthesis of azolypyridazinones **11a, b**. Compounds **3a, b** were converted into 1,2,4,5-dihydrotetrazines **4a, b** on refluxing in acetonitrile in the presence of ammonium acetate. Refluxing **3a** in dimethylformamide resulted in the formation of the 3-cyanoindazole **6**. Compound **3a wa**s converted to pyrazole **8** on treatment with the enaminone **7**, and to hydrazonyl bromide **9** on heating in dioxane/acetonitrile. Compound **12** was synthesized from the reaction of **10b** with ethanolic aqueous sodium hydroxide

Key words: azo compounds, aryl hydrazones, coupling, heterocycles, tetrazines

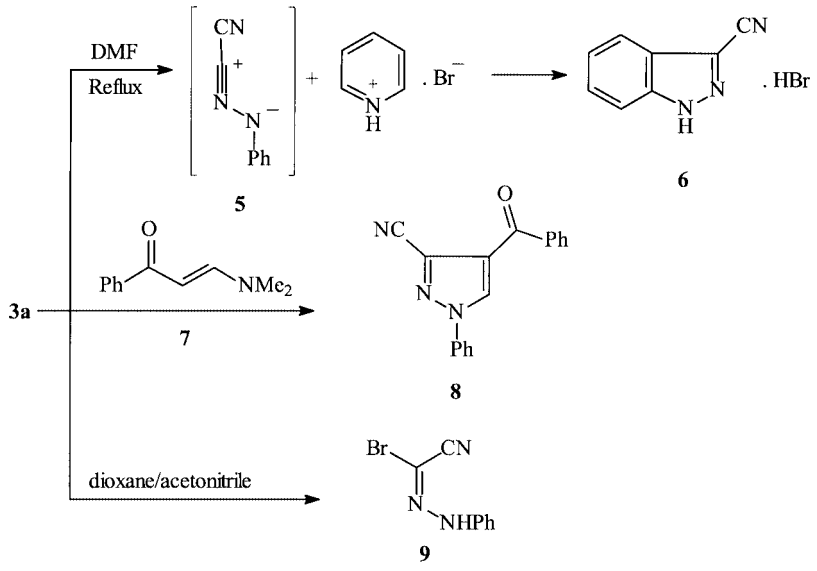
The reactivity of functionally substituted N-alkylpyridinium halides **1** towards carbon electrophiles has found, in the past, extensive utility in heterocyclic synthesis.[1-3] Recently, Katritzky et al.[4-6] investigated the reactivity of functionally substituted Nilális-alkylbenzotriazoles **2** towards carbon electrophiles. However, to the best of our knowledge, reactivity of **1** and **2** towards nitrogen electrophiles has not been investigated. In conjunction to our interest in developing efficient syntheses of functionally substituted heteroaromatics utilizing readily obtainable, inexpensive starting materials,[7,8] we investigated the reactivity of **1a, b** and **2a**–**c** towards aromatic diazonium salts, and achieved new syntheses of 1,2,4,5-tetrazines, 5-benzoyl-3-cyano-1-arylpyrazoles, 3-cyanoindazole, azolylpyridazinones as well as 2-bromo-2-phenylhydrazonoethanoicnitrile.

Thus, compounds **1a, b** (generated in situ from reaction of pyridine with bromoacetonitrile or 2-bromoacetophenone) coupled readily with benzenediazonium chloride to yield the phenylhydrazonylpyridinium bromides **3a, b** in good yields that were found to be stable upon long reflux in acetonitile. However, compounds **3a, b** were readily converted, almost quantitatively upon reflux in acetonitrile in the presence of ammonium acetate, into the 1,4-dihydro-1,2,4,5-tetrazines **4a, b** (Scheme 1). The reaction presumably proceeds via the intermolecular nucleophilic displacement of the pyridinium moiety, by the arylhydrazone nitrogen lone pair, or through the intermediacy of the nitrilimine **5** (Scheme 2), that dimerizes to give the 1,2,4,5-dihydrotetrazines **4a, b**. Compound **4b** was found to be identical with the authentic specimen prepared after the procedure described by Tewari, et al.[9]

Compound **3a** was converted into the cyanoindazole hydrobromide **6** when refluxed in dimethylformamide. The



Scheme 1



Scheme 2

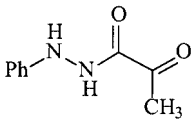
formation of this indazole derivative is believed to proceed through the intermediary of the nitrilimine **5**, which undergoes intramolecular cyclization into **6** (Scheme 2).

The fusion of **3b** with the enaminone **7** afforded the tetrazine **4b**. In a similar way, treating **3a** with **7** resulted in the formation of the pyrazole **8** (Scheme 2). The nitrilimine **5** is an assumable intermediate. However, possible initial addition of the hydrazone nitrogen to the double bond, followed by intramolecular nucleophilic displacement of the pyridinium moiety by active methylene in the formed adduct, and subsequent aromatization via dimethylamine elimination, cannot be overlooked.

Refluxing **3a** in a dioxane/acetonitrile mixture resulted in the formation of the hydrazonyl bromide **9** (Scheme 2), which is most likely formed via intermolecular displacement of the pyridinium moiety by the bromide ion. Although synthetic approaches to carbohydrazonyl bromides are well established, none can be readily adopted to generate **9**.[10]

Coupling **2a, b** with *p*-methoxybenzenediazonium chloride and with benzenediazonium chloride resulted in the formation of the arylhydrazones **10a** and **10b**, respectively, in excellent yields. However, these compounds proved to be stable under conditions that has led to the conversion of **3a** into compounds **6** and **8**. Compounds **10a, b** were converted into the corresponding pyridazines **11a, b**, upon treatment with ethyl cyanoacetate, in the presence of ammonium acetate and acetic acid (Scheme 3).

While **10a** was recovered unreacted on treatment with ethanolic aqueous sodium hydroxide, upon long reflux, compound **10b** afforded the pyruvic acid phenylhydrazone **12**.



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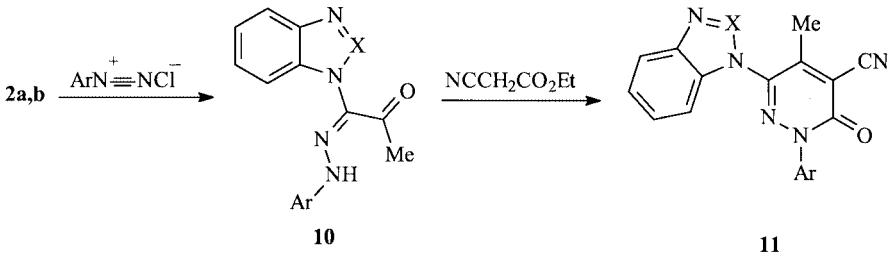
In conclusion, the arylhydrazones **3a, b** and **10a, b** can be considered as arylhydrazonyl halide synthetic equivalents and are thus promising for further utilities especially in dipolar cycloaddition reactions.



10 **11**

10-11a, X = N, Ar = $C_6H_4OCH_3$–p
b, X = CH, Ar = Ph

Scheme 3

All mps are uncorrected. IR spectra were recorded in KBr disks using a Shimadzu IR-740 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ac-80 spectrometer with DMSO-d_6 as solvent and TMS as internal standard; chemical shifts (δ) are reported in ppm. Mass spectra were measured on GS/MS INCOS XL Finnigan MAT. Microanalyses were performed on LECO CHNS-932. Compounds **2a, c** were prepared as described in the literature.[11,12]

Benzimidazo-1-ylacetone (2b)
A mixture of benzimidazole (1.18 g, 10 mmol), chloroacetone (0.92 g, 10 mmol) and Et_3N (1.01 g, 10 mmol) in toluene (20 mL) was refluxed for 5 h. The reaction mixture was allowed to cool, and the organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated to afford **2b**.

Yield: 1.29 g (74%), mp: 115−116 °C.

IR (KBr): ν = 1720 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.21 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 7.16−7.27 (m, 2H, Ar-H), 7.42−7.69 (m, 2H, Ar-H), 8.11 (s, 1H, H-2).

Anal: $C_{10}H_{10}N_2O$ (174.20): Calc C, 68.95; H, 5.79; N, 16.08. FoundC, 69.05; H, 5.79; N, 16.12.

Arylhydrazones 3a, b and 10a−b; General Procedure
A solution of aryldiazonium chloride (prepared as described earlier[13]) (10 mmol) at 0 °C was added to a solution of each of the N-alkylpyridinium halides **1a, b** (10 mmol) or the N-alkylbenzotriazoles **2a, b** (10 mmol) in EtOH (50 mL) containing sodium acetate (0.60 g). The reaction mixture was stirred at r.t. for 1 h and the solid product was collected by filtration and crystallized from EtOH.

2-Phenylhydrazono-2-pyrid-1-yliniumethanoicnitrile Bromide (3a)
Yield: 2.06 g (68%), mp: 181−182 °C.

IR (KBr): ν = 3241 (NH), 2219 (CN) cm^{-1}.

^{1}H NMR (DMSO): δ = 7.23−7.67 (m, 5H, Ar-H), 8.32−8.41 (m, 2H, pyridyl-H), 8.64−8.88 (m, 1H, pyridyl-H), 9.47−9.55 (d, 2H, pyridyl-H), 12.49 (br s, 1H, NH)

Anal: $C_{13}H_{11}N_4Br$ (303.26): Calc C, 51.48; H, 3.63; N, 18.48. Found C, 51.38; H, 4.01; N, 18.21.

1-Phenyl-2-pyrid-1-ylinium-2-phenylhydrazono-1-ethanone Bromide (3b)
Yield: 2.63 g (69%), mp: 172−173 °C.

IR (KBr): ν = 3256 (NH), 1668 (C=O) cm^{-1}.

^{1}H NMR (DMSO): δ = 7.14−7.70 (m, 10H, Ar-H), 8.46−8.90 (m, 3H, pyridyl-H), 9.69−9.78 (d, 2H, pyridyl-H), 12.60 (br s, 1H, NH)

Anal: $C_{19}H_{16}N_3OBr$ (382.20): Calc. C, 59.68; H, 4.18; N, 10.99. Found C, 59.45; H, 4.21; N, 10.92.

1-(Benzotriazol-1-yl)-1-*p*-methoxyphenylhydrazonopropan-2-one (10a)
Yield: 2.37 g (77%), mp: 141−142 °C.

IR (KBr): ν = 3210 (NH), 1663 (C=O) cm^{-1}.

^{1}H NMR (DMSO): δ = 2.72 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.83−6.94 (m, 2H, Ar-H), 7.25−7.37 (m, 5H, Ar-H), 7.69−7.87 (m, 1H, Ar-H), 10.13 (br s, 1H, NH).

Anal: $C_{16}H_{15}N_5O_2$ (309.32): Calc C, 62.12; H, 4.89; N, 22.64. Found C, 62.10; H, 5.06; N, 22.60.

1-(Benzimidazol-1-yl)-1-phenylhydrazonopropan-2-one (10b)
Yield: 1.75 g (63%), mp: 246−247 °C.

IR (KBr): ν = 3212 (NH), 1678 (C=O) cm^{-1}.

^{1}H NMR (DMSO): δ = 2.59 (s, 3H, CH_3), 7.13−7.39 (m, 8H, Ar-H), 7.62−7.79 (m, 1H, Ar-H), 8.20 (s, 1H, benzimidazolyl-H), 10.80 (br s, 1H, NH).

Anal: $C_{16}H_{14}N_4O$ (278.30): Calc C, 69.05; H, 5.07; N, 20.13. Found C, 68.95; H, 5.14; N, 19.86.

Tetrazines 4a, b; General Procedure
A suspension of each of compounds **3a, b** (10 mmol) in MeCN (30 mL), was treated with ammonium acetate (1 g). The reaction mixture was refluxed for 1 h, then evaporated under vacuo to half of its volume. The solid product was collected by filtration and crystallized from EtOH.

1,4-Diphenyl-1,4-dihydro-1,2,4,5-tetrazine-3,6-dicarbonitrile (4a)
Yield: 2.40 g (84%), mp: 134−135 °C.

IR (KBr): ν = 2241 (CN) cm^{-1}.

^{1}H NMR (DMSO): δ = 7.29−7.42 (m, 10H, Ar-H).

Anal: $C_{16}H_{10}N_6$ (286.29): Calc C, 67.13; H, 3.49; N, 29.37. Found C, 67.08; H, 3.70; N, 29.13.

3,6-Dibenzoyl-1,4-dihydro-1,4-diphenyl-1,2,4,5-tetrazine (4b)
Yield: 3.37 g (76%), mp: 189−190 °C. (Lit. mp: 196 °C)

IR (KBr): ν = 1660 (C=O) cm^{-1}.

^{1}H NMR (DMSO): δ = 7.18−7.34 (m, 10H, Ar-H), 7.57−7.66 (m, 6H, Ar-H), 7.96−8.06 (m, 4H, Ar-H),

Anal: $C_{28}H_{20}N_4O_2$ (444.47): Calc C, 75.65; H, 4.54; N, 12.61. Found C, 75.46; H, 4.73; N, 12.41.

3-Cyanoindazole Hydrobromide (6)
A suspension of compound **3a** (10 mmol) in DMF (30 mL), was refluxed for 3 h, then evaporated under vacuo to half of its volume. The solid product was collected by filtration and crystallized from DMF.

Yield: 1.34 g (60%), mp: 139−140 °C.

IR (KBr): ν = 3241 (NH), 2221 (CN) cm^{-1}.

^{1}H NMR (DMSO): δ = 7.04−7.37 (m, 4H, Ar-H), 11.20 (br s, 1H, NH)

MS: *m/z* = 144 (M^+).

Anal: $C_8H_6N_3Br$ (224.14): Calc C, 42.84; H, 2.67; N, 18.75. Found C, 42.51; H, 2.48; N, 18.98.

4-Benzoyl-1-phenylpyrazole-3-carbonitrile (8)
A mixture of **3a** (3.03 g, 10 mmol) and the enaminone **7** (1.75 g, 10 mmol) was heated at 250°C for 10 min. The reaction mixture was left to cool, then triturated with MeOH and precipitated by adding a few drops of H_2O. The solid product, so formed, was collected by filtration and crystallized from the EtOH.

Yield: 1.85 g (68%), mp: 136−137 °C.

IR (KBr): ν = 2215 (CN), 1644 (C=O) cm^{-1}.

^{1}H NMR (DMSO): δ = 7.02−8.10 (m, 11 H).

Anal: $C_{17}H_{11}N_3O$ (273.28): Calc C, 74.71; H, 4.06; N, 15.38. Found C, 74.83; H, 4.19; N, 15.01.

2-Bromo-2-phenylhydrazonoethanoicnitrile (9)
A suspension of compound **3a** (10 mmol) in a mixture of dioxane/MeCN (30 mL, 3:1) was refluxed for 3 h, then evaporated under vacuo to half of its volume. The solid product was collected by filtration and crystallized from MeCN.

Yield: 1.47 g (66%), mp: 125−126 °C.

IR (KBr): ν = 3235 (NH), 2220 (CN) cm^{-1}.

^1H NMR (DMSO): δ = 7.26−7.78 (m, 5H, Ar-H), 12.67 (br s, 1H, NH)

MS: *m/z* = 223 (M^+−1).

Anal: $C_8H_6N_3Br$ (224.05): Calc C, 42.84; H, 2.67; N, 18.75. Found C, 43.01; H, 2.93; N, 18.66.

Pyridazinones 11a, b; General Procedure
A mixture of ethyl cyanoacetate (1.13 g, 10 mmol), ammonium acetate (4 g) and HOAc (0.6 mL) was treated with either of the aryl hydrazones **10a, b** (10 mmol). The reaction mixture was heated at 220°C for 15 min, left to cool, then triturated with EtOH. The solid product, so formed, was collected by filtration and crystallized from EtOH.

3-(Benzotriazol-1-yl)-1,6-dihydro-4-methyl-6-oxo-1-p-methoxyphenylpyridazine-5-carbonitrile (11a)
Yield: 2.32 g (65%), mp: 174−175 °C.

IR (KBr): ν = 2205 (CN), 1667 (C=O) cm^{-1}.

^1H NMR (DMSO): δ = 2.66 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.91−7.03 (m, 2H, Ar-H), 7.54−7.67 (m, 5H, Ar-H), 8.08−8.20 (m, 1H, Ar-H).

Anal: $C_{19}H_{14}N_6O_2$ (358.39): Calc C, 63.68; H, 3.94; N, 23.45. Found C, 63.86; H, 4.00; N, 23.45.

3-(Benzimidazol-1-yl)-1,6-dihydro-4-methyl-6-oxo-1-phenylpyridazine-6-carbonitrile (11b)
Yield: 1.99 g (61%), mp: 173 °C.

IR (KBr): ν = 2233 (CN), 1678 (C=O) cm^{-1}.

^1H NMR (DMSO): δ = 2.48 (s, 3H, CH_3), 7.28−8.02 (m, 8H, 7H, Ar-H, and 1H, benzimidazolyl-H), 8.18−8.35 (m, 2H, Ar-H).

Anal: $C_{19}H_{13}N_5O$ (327.33): Calc C, 69.71; H, 4.00; N, 21.40. Found C, 69.82; H, 4.21; N, 21.37.

Pyruvic Acid Phenylhydrazide (12)
A suspension of compound **4b** (10 mmol) in ethanolic aq NaOH 5% (20 mL, 2:1) was refluxed for 3 h. Neutralization with HCl (2.0 M) gave the desired product, that was collected by filtration and crystallized from EtOH.

Yield: 0.99 g (74%), mp: 259−260 °C.

IR (KBr): ν = 1678 (C=O) cm^{-1}.

^1H NMR (DMSO): δ = 2.34 (s 3H, CH_3), 7.85−8.05 (m, 5H, Ar-H), 10.26 (s, 1H, NH), 11.95 (s, 1H, NH).

Anal: $C_9H_{10}N_2O_2$ (178.19): Calc C, 60.66; H, 5.66; N, 15.72. Found C, 60.99; H, 5.83; N, 15.45.

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