Arylhydrazonals as aldehyde components in Baylis-Hillman reaction: synthesis of 5-hydroxy-2,3,4,5-tetrahydropyridazine-4-carbonitrile and 6,7,8,8a-tetrahydrocinnolin-5(1*H*)-one

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Abstract
3-Oxo-2-arylhydrazonals reacted with acrylonitrile to yield hydroxyl tetrahydropyridazine derivatives and with cyclohexenone to yield tetrahydrocinnoline.
Keywords: 3-Oxo-2-arylhydrazonals, hydroxypyridazine, dihydropyridazine, hexahydrocinnoline

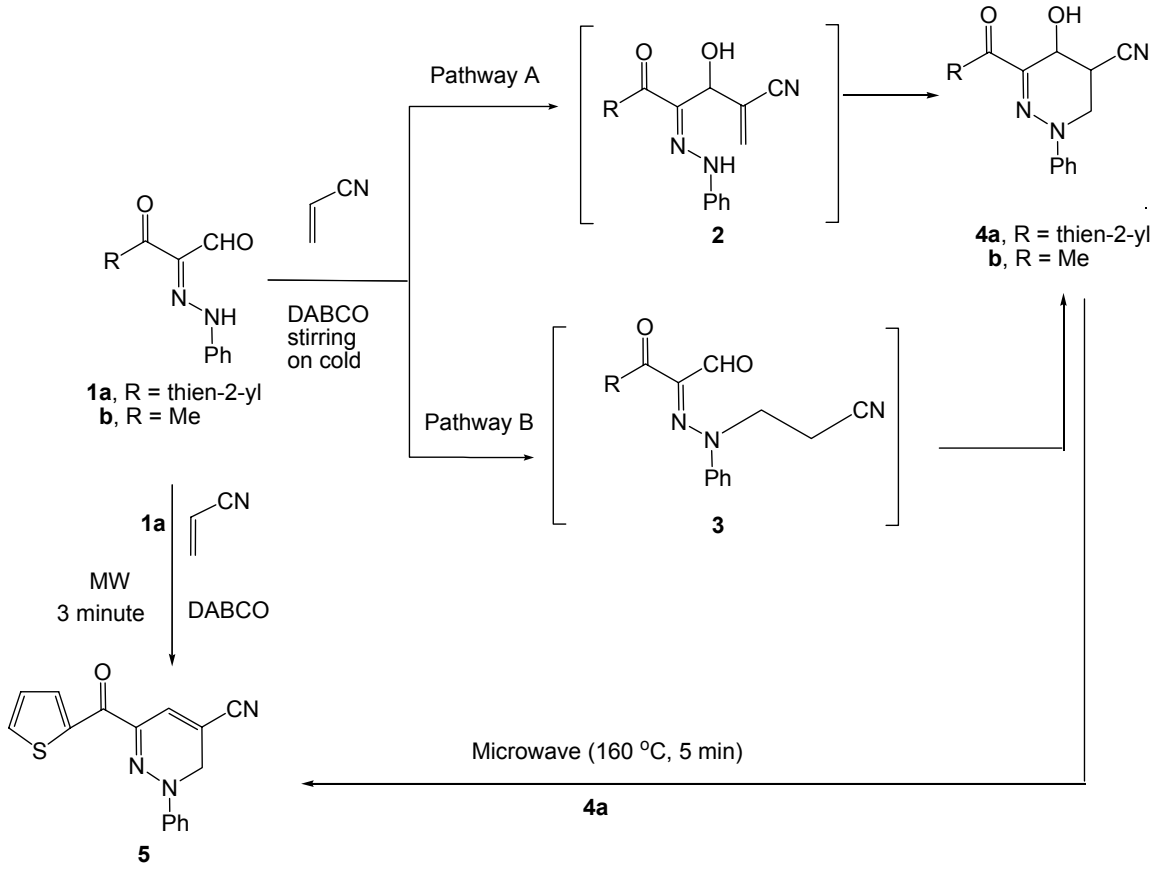
Introduction

Arylhydrazonals are versatile reagents and their chemistry is receiving considerable interest.[1-10] In the past our group could successfully utilitized arylhydrazonals as precursors to pyridazines and pyrazoles with unique substitution pattern.[11-16]

Results and Discussion

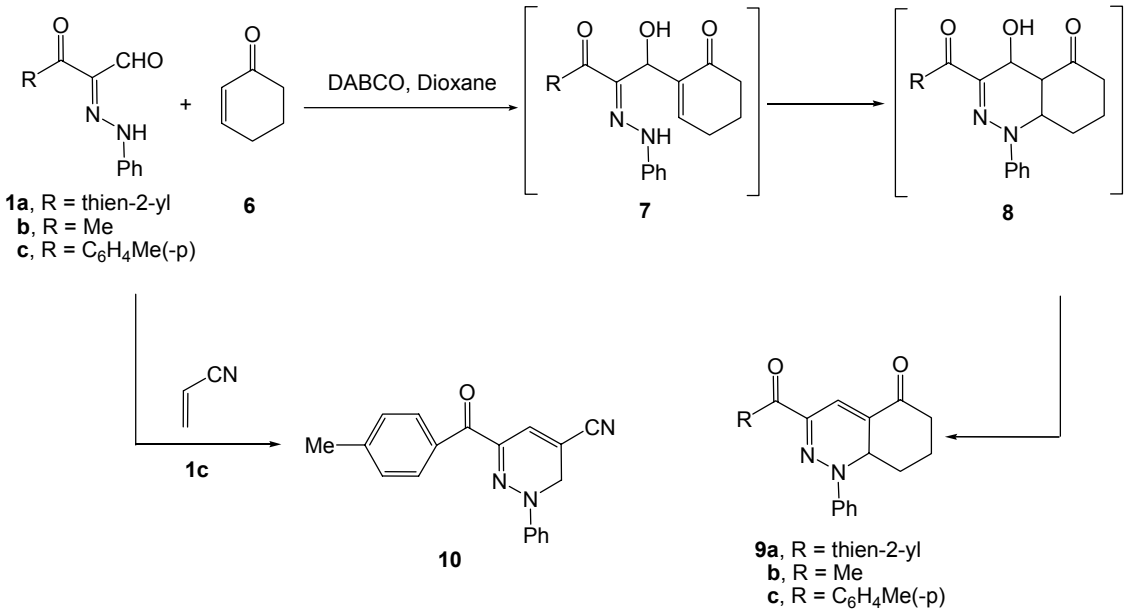
Very recently one of us has reported the first utility of the aryl hydrazonals as the aldehyde components in Baylis-Hillman reaction under microwave irradiation.[17] In conjunction of this work we tried the reactivity of arylhydrazonals toward α,β-unsaturated nitriles and ketones utilizing the conventional Baylis-Hillman reaction conditions. In this work, not only intermediate Baylis-Hillman adducts could be isolated (characterized in some cases) but also a novel reactivity pattern is achieved. Thus reacting 3-oxo-2-phenylhydrazono-2-yl-propionaldehydes **1a,b** with acrylonitrile in presence of DABCO (1,4-diazabicyclo[2.2.2]octane) as a catalyst and dioxane as a solvent, resulted in the formation of compound **4** which could be formed through the Baylis-Hillman intermediate **2** (*Pathway A*) (cf. scheme 1). Compound **4** can be also formed *via* intermediate **3** that results most likely *via* initial addition of the hydrazone NH to the

electrophilic double bond in acrylonitrile followed by normal aldol condensation (*Pathway B*) (cf. scheme 1). The structure of compound **4** was confirmed based on spectroscopic tools. Thus, the mass spectrum of **4a** revealed molecular ion peak as base peak at m/z 311; IR showed OH at 3340 cm^{-1}; ^{1}H NMR revealed doublet signals at 3.61 and 6.40 for pyridazine H5 and OH respectively, multiplet signal at 3.87 for pyridazine H4 and doublet of doublet signal at 4.51 and 4.94 for pyridazine H3. Also ^{13}C NMR showed three SP^3 carbons. Heating compound **4** in microwave for five minutes resulted in the formation of 1, 6-dihydropyridazine derivative **5**. Product **5** was previously obtained on reacting **1** with acrylonitrile in microwave for three minutes.[17]



Scheme 1

Compounds **1a-c** reacted with 2-cyclohexen-1-one **6** to yield tetrahydro-*1H*-cinnolin-5-one derivative **9a-c** respectively that are formed most likely *via* intermediacy of **7** and **8**. Trials to isolate the Baylis-Hillman adduct **7** or **8** failed (cf. scheme 2). The structure of the resultant compound **9** has been confirmed by spectral data. Similarly, compound **1c** reacted with acrylonitrile to yield the dihydropyridazine **10**. Attempts to isolate the intermediate hydroxy compounds in these reactions failed (cf. scheme 2).



Scheme 2

Experimental Section

General Procedures. The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a FTIR unit Bruker-vector 22 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 as solvent at 400 MHz on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GMMS -QP-1000 EX mass spectrometer at 70 eV.

General method fo synthesis of pyridazine derivatives (4, 5 and 10), cinnoline derivatives 9a-c

Method A (for **4**, **5**, **9a-c** and **10**). A mixture of arylhydrazonal derivatives **1** (1 mmol), acrylonitrile or cyclohexenone (2 mmol) and DABCO (1 mmol) was mixed and stirred for 4-7 days in dioxane (the reaction progress was followed using TLC). The mixture was then poured onto water and acidified with dilute hydrochloric acid. Solid products were crystallized from proper solvents.

Method B (for **5**, **9a-c** and **10**). A mixture of arylhydrazonal derivatives **1** (1 mmol), acrylonitrile or cyclohexenone (2 mmol) and DABCO (1 mmol) in a sealed vessel was placed in a single mode cavity Explorer Microwave Synthesizer and irradiated at temperature 160 ^{o}C for 5 min. The reaction contents was then poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from proper solvent.

5-Hydroxy-2-phenyl-6-(thiophene-2-carbonyl)-2,3,4,5-tetrahydropyridazine-4-carbonitrile (4a). Yellow crystals from ethanol, yield (73%), mp: 162-164˚C; MS: m/z = 311 (53.7%), 312 (18.9%), 293 (7.8%), 200 (17%), 111 (100%); IR (KBr): 3340 (OH), 2248 (CN), 1645 (CO); 1H NMR (400 MHz, DMSO-d6): δ 3.61 (d, 1H, pyridazine H5), 3.87 (m, 1H, pyridazine H4), 4.51 (dd, 1H, pyridazine H3), 4.94 (dd, 1H, pyridazine H3), 6.40 (d, 1H, OH), 7.19 (m, 1H, Ph-H), 7.26 (m, 1H, thiophene-H4), 7.47-7.55 (m, 4H, Ph-H) 8.02 (d, 1H, thiophene-H3), 8.05 (d, 1H, thiophene-H5). ^{13}C NMR (100 MHz, DMSO-d6): δ: 18.0, 26.6, 55.4, 115.6, 116.2 (CN), 120.8, 121.1, 126.2, 128.2, 129.3, 131.0, 134.2, 136.6, 187.6 (CO). *Anal.* Calcd. for $C_{16}H_{13}N_3O_2S$ (311.36) C, 61.72; H, 4.21; N, 13.50. Found: C, 61.32; H, 4.32; N, 13.38.

6-Acetyl-5-hydroxy-2-phenyl-2,3,4,5-tetrahydropyridazine-4-carbonitrile (4b). Yellow crystals from ethanol, yield (68%), mp 193-195 ºC; MS: m/z = 243(100 %), 244 (16.7%), 225 (13.5%), 224 (5.8%), 200 (17.9%); IR: 3350 (OH), 2245 (CN), 1655 (CO); ^{1}H NMR (400 MHz, DMSO-d6): δ 2.48 (s, 3H, CH_3), 3.52 (d, 1H, pyridazine H5), 3.69 (m, 1H, pyridazine H4), 4.42 (dd, 1H, pyridazine H3), 4.71 (dd, 1H, pyridazine H3), 6.40 (d, 1H, OH), 7.13-7.53 (m, 5H, Ph-H); ^{13}C NMR (100 MHz, DMSO-d6): δ:18.5 (CH_3), 24.1, 27.2, 54.4, 115.9 (CN), 118.0, 123.5, 129.3,138.7, 145.2, 194.8 (CO). *Anal.* Calcd. for $C_{13}H_{13}N_3O_2$ (243.26) C, 64.19; H, 5.39; N, 17.27. Found: C, 64.43; H, 5.28; N, 17.45.

2-Phenyl-6-(thiophene-2-carbonyl)2,3-dihydro-pyridazine-4-carbonitrile (5). Yellow crystals from ethanol, yield (88%), mp 156-58 ºC; MS: m/z = 293 (M, 80%), 174 (10%), 111 (100%); IR: 2217 (CN), 1614 (CO); ^{1}H NMR (400 MHz, DMSO-d6): δ 4.86 (s, 2H, pyridazine-H6), 7.27 (m, 2H, Ar-H), 7.43 (s, 1H, pyridazine-H4), 7.57-7.52 (m, 4H, Ar-H and thiophene-H), 8.08 (m, 2H, Ar-H and thiophene-H); ^{3}C NMR (100 MHz, DMSO-d6): δ 44.6 (CH_2), 102.6 (CN) 117.2, 117.9, 125.7, 127.5, 128.3, 129.9, 135.3, 136.5, 137.2, 138.7, 144.3, 178.0 (CO). *Anal.* Calcd. for $C_{16}H_{11}N_3OS$ (293.34) C, 65.51; H, 3.78; N, 14.32. Found: C, 65.33; H, 3.65; N, 14.61.

1-Phenyl-3-(thiophene-2-carbonyl)-6,7,8,8a-tetrahydro-*1H*-cinnolin-5-one (9a). Orange crystals from ethanol, yield (84%), mp =292-294˚C; MS: m/z = 335 (8.6%), 336 (20.4%), 111 (100%); IR (KBr): 1705, 1630 (2CO); ^{1}H NMR (400 MHz, DMSO-d6): δ 0.83 (m, 2H, H7), 1.83 (m, 2H, H8), 1.9 (m, 2H, H6) 4.8 (m, 1H, H8a), 7.01(s, 1H, H4), 7.19-8.03(m, 8H, Ph and thiophene-H). ^{13}C NMR (100 MHz, DMSO-d6): δ 18.8, 28,7, 37.9, 55.4, 115.6, 116.2, 120.8, 121.1, 126.2, 127.5, 128.3, 129.2, 131, 134.3, 135.4, 138.6, 177 (CO), 197.6 (CO). *Anal.* Calcd. for $C_{19}H_{16}N_2O_2S$ (336.41) C, 67.84; H, 4.79; N, 8.33. Found: C, 67.61; H, 4.92; N, 8.18.

3-Acetyl-1-phenyl-6,7,8,8a-tetrahydrocinnolin-5(1*H*)-one (9b). Orange crystals from ethanol, yield (88%), mp =184-186˚C; MS: m/z = 268 (3.8%), 269 (4.6%), 225 (3.1%); IR (KBr): 1660, 1596 (2 CO);^{1}H NMR (400 MHz, DMSO-d6): δ 1.39 (m, 2H, H7), 2.2 (m, 4H, H6, H8), 2.46 (s, 3H, CH_3), 4.8 (m, 1H, H8a), 6.90(s, 1H, pyridazine-H4), 7.10-7.61(m, 5H, Ph-H). *Anal.* Calcd. for $C_{16}H_{16}N_2O_2$ (268.31) C, 71.62; H, 6.01; N, 10.44. Found: C, 71.82; H, 6.24; N, 10.63.

3-(4-Methyl-benzoyl)-1-phenyl-6,7,8,8a-tetrahydro-*1H*-cinnolin-5-one (9c). Orange solid from ethanol, yield (86%), mp: 252-254 ºC; MS: m/z = 344 (21.6%), 345 (5.6%), 119 (100%); IR (KBr): 1703, 1629 (2CO), ^{1}H NMR (400 MHz, DMSO-d6): 1.45 (m, 2H, H7), 2.31-2.38 (m, 4H, H6, H8), 2.41 (s, 3H, CH_3), 4.82 (m, 1H, H8a), 7.19(s, 1H, pyridazine-H), 7.25-7.85(m, 9H,

Ar-H). ^{13}C NMR (100 MHz, DMSO-d6): δ 21.0, 29.8, 36.5, 54.9, 108.2, 112.3, 119.3, 123.0, 124.8, 126.0, 129.3, 134.5, 138.9, 141.9, 143.8, 147.2, 187.7 (CO), 197 (CO). *Anal.* Calcd. for $C_{22}H_{20}N_2O_2$ (344.41) C, 76.72; H, 5.85; N, 8.13. Found: C, 76.86; H, 5.93; N, 8.24.

6-(4-Methyl-benzoyl)-2-phenyl-2,3-dihydro-pyridazine-4-carbonitrile (10). Yellow solid from ethanol, yield (84%), mp =178-180ºC; MS: m/z = 301 (76.3%), 303 (15.4%), 119 (100%); IR (KBr): 2214.13 (CN), 1704 (CO); ^{1}H NMR (400 MHz, DMSO-d6): δ 2.39 (s, 3H, CH_3), 4.81 (s, 2H, pyridazine-H6), 7.21 (m, 1H, Ar-H), 7.33 (s, 1H, pyridazine-H4), 7.35-7.42 (m, 4H, Ar-H), 7.45 (d, 2H, Ar-H, *J* = 7.8 Hz), 7.83 (d, 2H, Ar-H, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, DMSO-d6): δ 21.0 (CH_3), 43.6, 102.1, 116.6 (CN), 120.8, 124.7, 127.6, 128.5, 129.3, 130.0, 133.8, 136.5, 142.4, 143.8, 187.0 (CO). *Anal.* Calcd. for $C_{19}H_{15}N_3O$ (301.12) C, 75.73; H, 5.02; N, 13.94 . Found: C, 75.54; H, 5.13; N, 13.78.

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