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A new facile method for preparation of heterocyclic α-iminonitriles and α-oxoacetic acid from heterocyclic aldehydes, *p*-aminophenol, and sodium cyanide

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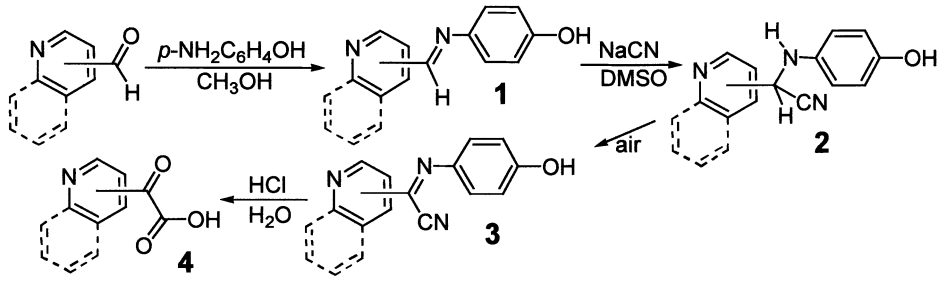
Abstract—Very efficient, simple, and high yield procedures for the transformation of heterocyclic aldehydes into heterocyclic methylidene-*p*-hydroxyanilines, heterocyclic α-iminonitriles, and finally into heterocyclic α-oxoacetic acids were described. Considering that many of these compounds have biological activity, the synthetic methodology was optimized using readily available, inexpensive starting materials, and the purification of the product involved only simple crystallization.

Aromatic imines, better known as Schiff bases, can easily be prepared from corresponding aromatic aldehydes and substituted anilines by acid-catalyzed condensation in an inert organic solvent.[1] Heteroaromatic imines (Schiff bases) containing the phenol moiety are of particular interest due to their wide biological properties, such as antioxidative and anticancer properties.[2] They are also precursors for the preparation of other biologically important compounds. For instance, reduced and sulfonated heterocyclic Schiff bases have antiplasmodic activity,[3] while acylated Schiff bases made from heterocyclic aldehydes and *p*-aminophenol form liquid crystals.[4] Our own preliminary results with tribarbiturates derived from these valuable intermediates show promising immune-modulating activity. Therefore, it is very important to have a simple and efficient method for the preparation of these compounds. Here we present an exceptionally simple procedure, applicable to multi grams if not to multi kilogram preparation of these valuable materials. The procedure involves simple mixing of both the heterocyclic aldehyde and *p*-aminophenol in methanol as a solvent, refluxing the resulting reaction mixture, and crystallization of the solid product from methanol.[5] In this way heterocyclic imines were prepared in high purity and in almost quantitative yields (Table 1).

α-Iminonitriles as structural derivatives of the mentioned Schiff bases also have interesting biological activities.[6] There are many synthetic procedures for the preparation of aryl(arylimino)acetonitriles but only a few include heterocyclic aromatic compounds, and the procedures for preparation are not so simple. For instance, aromatic amides were converted into α-imi-



Scheme 1. Transformation of heterocyclic aldehyde into heterocyclic α-oxoacetic acid.

Keywords: Schiff bases; α-iminonitriles; α-ketoacids; α-oxoacetic acids; heterocyclic benzylideneanilines.

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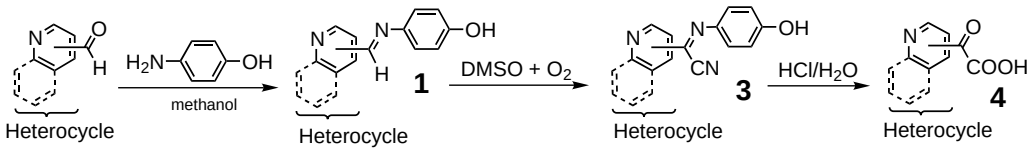
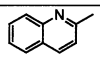
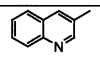
Table 1. The isolated yields (%) of imines (**1**), α-iminonitriles (**3**), and α-oxoacetic acids



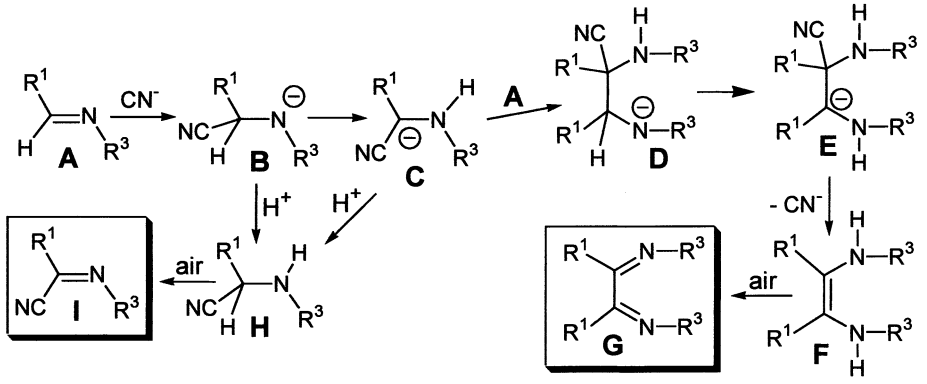
aldehyde	1	Yield	3	Yield	4	Yield
	**1a**	95	**3a**	83	**4a**	66
	**1b**	93	**3b**	87	**4b**	70
	**1c**	97	**3c**	81	**4c**	73
	**1d**	92	**3d**	82	**4d**	81
	**1e**	96	**3e**	91	**4e**	80
	**1f**	97	**3f**	92	**4f**	75
	**1g**	94	**3g**	83	**4g**	63

nonitriles through reactions with thionyl chloride followed by substitution with copper(I) cyanide.[7] These compounds are also prepared from aromatic aldehydes through thioethers,[8] aldimines,[9] α-iminochlorides under phase-transfer catalysis,[10] etc.

Considering the structural similarity between Schiff bases and α-iminonitriles (Scheme 1) one would expect that simple substitution of the hydrogen of the carbon–nitrogen double bond (compound **1**, Scheme 1) would result in the preparation of the corresponding α-iminonitrile. This is actually accomplished through the addition of cyanogen bromide, followed by elimination of hydrogen bromide.[11] One can envision a similar reaction path where the addition of hydrogen cyanide is the first step followed by the elimination of the hydrogen molecule via oxidation. There are also some studies that involve the cyanide anion mediated coupling of aromatic Schiff bases into the corresponding α,α′-dianilino derivatives.[12] This approach was used for the preparation of substituted benzyl derivatives[13] with limited application to heterocyclic aromatic diketones.[14] According to the proposed mechanism, the cyanide anion was added to the carbon–nitrogen double bond of the imine, followed by the 1,2-hydrogen shift that produced a new carbon nucleophile **C** which adds to the carbon–nitrogen double bond of the second imine molecule **A**, generating a new anion **D** (Scheme 2). Anion **D** rearranges into the second carbon nucleophile **E** that eliminates the cyanide ion to form dienamine **F**. The dienamine **F** oxidizes in air to the final product of the cyanide-catalyzed imine dimerization **G** (Scheme 2).

One can speculate that by a slight change of the reaction conditions the final outcome of the reaction might be replacement of the imine hydrogen by the cyanide group to produce α-iminonitriles. That can be accomplished if the production of intermediate **D** is halted by protonation of either intermediate **B** or intermediate **C** (Scheme 2). Thus, the secondary amine **H** produced should be possible to air oxidize into the corresponding α-iminonitrile **I** in the same manner as dienamine **F**. Our attempt to control the reaction by slow injection of acid into the reaction mixture produced a small amount of the desired product, but the exact procedure was hard to reproduce. The best results were obtained if the reaction was performed in weak acid media. Our experiments reveal that phenols with $pK_a \sim 10$ are the best acid for this reaction. Even better results are obtained if phenol is a part of the imine structure.

To demonstrate the efficiency of this reaction we have performed a series of NMR experiments with heterocyclic imines containing the phenolic moiety. Due to its ^{1}H NMR spectra simplicity we selected the reaction with imine **1c** to demonstrate transformation of the heterocyclic imine into the heterocyclic α-iminonitrile with a phenolic moiety. The 10 mM DMSO-d_6 solution of **1c** was treated with 11 mmol of sodium cyanide and NMR spectra were recorded every 5 min (Fig. 1). In



Scheme 2. Cyanide anion-promoted oxidative dimerization of Schiff bases.

approximately 30 min at room temperature 1/3 of the starting material was transformed into secondary amine **2c**. After 2 h the reaction was practically completed (Fig. 1). If the NMR sample is exposed to air for a few hours then the secondary amine **2c** is almost completely oxidized into α-iminonitrile **3c** (Fig. 1). The same procedure[15] was applied for high yield preparation of additional heterocyclic α-iminonitriles (Table 1).

To fully confirm the structural properties of heterocyclic α-iminonitriles we performed X-ray structural analysis of the α-iminonitrile prepared from 4-quinolinecarbaldehyde (Fig. 2). The mono-crystal for the X-ray analysis was obtained by slow crystallization of **3f** from methanol.[16] Determined structural properties agree well with the proposed structure of α-iminonitriles. The C(11)–N(12) and the C(19)–N(20) bond dis-

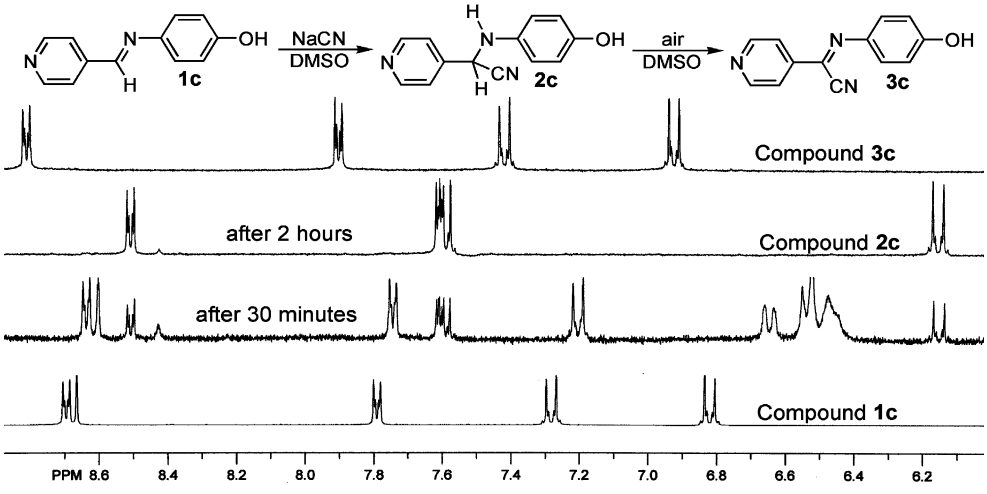


Figure 1. The NMR following the oxidative cyanide addition.

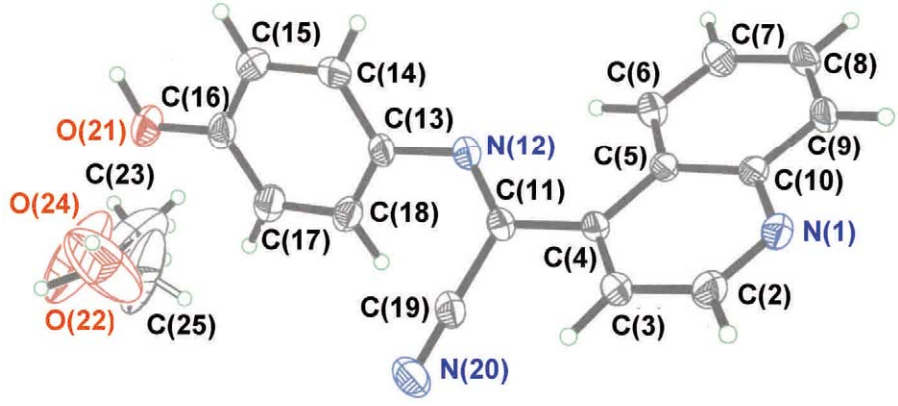


Figure 2. The ORTEP drawing of **3f** with one methanol molecule.

tances of 1.2751(15) and 1.1418(15) Å, respectively, indicate the double and triple C–N bonds in the α-iminonitriles. Both aromatic moieties (quinoline and phenol) are slightly puckered in regard to the α-iminonitrile moiety. For instance, the C(3)–C(4)–C(5)–C(6) torsion angle of the quinoline moiety is 176.77(12)°, while the same kind of torsion angle of the phenol moiety C(18)–C(13)–C(14)–C(15) is 3.6(2)°. Both rings form an angle of ~25° with C=N α-iminonitrile moiety.[17]

α-Iminonitriles are compounds that should be easy to hydrolyze to the desirable heterocyclic-α-oxoacetic acids.[18] These-α-oxoacetic acids either have biological activity or they are key intermediates for larger organic molecules with pharmaceutical or industrial applications.[19] In addition to the hydrolysis of heterocyclic α-iminonitriles for the formation of α-oxoacetic acids, there are some other methods of preparation, such as base hydrolysis of heterocyclic α-oxoamides,[20] potassium cyanide and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)-catalyzed carbonation of heterocyclic aldehydes,[21] a low yield (10–30%) $PdCl_2(PPh_3)_2$-catalyzed CO carbonylation of heterocyclic halides in the presence of H_2O and Et_3N.[22] Our approach is exceptionally simple, it involves stirring an aqueous hydrochloric acid suspension of heterocyclic α-iminonitrile followed by the separation of heterocyclic α-oxoacetic acid from *p*-aminophenol.[23] The isolated yields are very high (Table 1).

It can be concluded that a very systematic study of the transformation of heterocyclic aldehydes into heterocyclic Schiff bases, heterocyclic α-iminonitriles, and finally into heterocyclic α-oxoacetic acid was performed. The resulting synthetic methods are exceptionally simple, applicable to multi grams if not to multi kilograms production of industrially and biologically valuable materials.

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5. **General procedure for preparation of heterocyclic imines**. *Preparation of 4-(pyridin-4-ylmethyleneamino)phenol (**1**).* A mixture of 4-pyridinecarboaldehyde (2.67 g; 25 mmol) and 4-aminophenol (2.73 g; 2.5 mmol) in methanol (500 ml) was refluxed for 2 h. The solvent was reduced to 1/10 of its original volume. The resulting suspension was cooled in an ice-water bath. The solid was separated by filtration, washed with cold methanol (3×25 ml) and dried at 80°C for a 0.5 h resulting in pure compound in 97% yield (4.8 g). ^{1}H NMR (DMSO-d_6) δ 9.664 (1H, s, OH), 8.695 (2H, d, $J=6.3$ Hz, pyridine 2-H), 8.665 (1H, s, CH=N), 7.791 (2H, d, $J=6.0$ Hz, pyridine 3-H), 7.283 (2H, d, $J=8.7$ Hz, phenol 3-H), and 6.820 (2H, d, $J=9.0$ Hz); ^{13}C NMR (DMSO-d_6), 153.784, 151.615, 146.873, 139.545, 138.119, 119.631, 118.417, and 112.356 ppm; MS (EI) *m*/*z* 199 ($M+1^+$, 20%), 198 (M^+, 100%), 197 ($M-1^+$, 40%), 120 ($M-C_5H_4N^+$, 30%), 93 ($CH_3C_5H_4N^+$, 15%), and 79 (C_5H_5N, 10%).
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15. **General procedure for preparation of heterocyclic α-iminonitriles**. *Preparation of (4-hydroxyphenylimino)pyridin-4-ylacetonitrile (**3c**).* A dimethyl sulfoxide (100 ml) solution of 4-(pyridin-4-ylmethyleneamino)phenol (1.98 g; 10 mmol) and sodium cyanide (550 mg; 11 mmol) was stirred at room temperature for 3 h. The solution immediately turned deep red. The solvent was evaporated at reduced pressure (0.03 mmHg) with minimal heating (water bath temperature 40–50°C). A dark red solid residue was slurred in tetrahydrofuran (100 ml) and filtered through a short column (6×3 cm) of silica gel. The silica gel was washed with tetrahydrofuran (6×50 ml). A combined THF solution was evaporated to solid. The solid residue was slurred in methanol (50 ml) and the resulting suspension was heated at 50°C for approximately 10 min, cooled down in an ice-water bath and the solid was separated by filtration and washed with ice cooled methanol (3×20 ml). The product yield was 89% (1.8 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (1H, broad singlet, OH), 8.815 (2H, d, $J=6.0$ Hz, pyridine 2-H), 7.903 (2H, d, $J=6.4$ Hz, pyridine 3-H), 7.418 (2H, d, $J=8.8$ Hz), and 6.924 ppm (2H, d, $J=8.8$ Hz). ^{13}C NMR (400 MHz, DMSO-d_6) δ 155.336, 147.077, 137.163, 125.610, 120.614, 117.096, 112.355, and 107.983 ppm; MS (EI) *m*/*z* 223 (M+, 20%) and 222 (M−1+, 100%). Anal. calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.87; H, 18.75; N, 4.13%.
16. X-Ray structure determination was performed on Bruker SMART 1KCCD automated diffractometer. Crystals of compound **3f** were obtained by crystallization from methanol by allowing slow solvent evaporation. All reagents and solvents were purchased from Aldrich and used without prior purification. X-Ray single crystal structure determination of compound **3f** at 155(2) K. *Crystal data*: $C_{17}H_{11}N_3O_1$ 0.744(5) [CH_3OH], $M_r=297.08$, monoclinic, space group $C2/c$, $a=19.821(2)$, $b=7.7771(8)$, $c=19.630(2)$ Å, $\beta=105.086(2)°$, $V=2921.6(5)$ Å^3, $Z=8$, ρ_{calcd} 1.351 Mg m^{-3}, $F_{000}=1243$, wavelength (λ) = 0.71073 Å, absorption coefficient (μ) = 0.090 mm^{-1}.

Data collection and reduction: crystal size: 0.25×0.55×0.60 mm, theta range: 2.13–33.09°, index ranges: $-29 \leq h \leq 24$, $-7 \leq k \leq 11$, $-30 \leq l \leq 30$, reflections collected: 13663, independent reflections: 5388 [$R_{int} = 0.0295$], refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 5388/253/293. Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0465$, w$R_2 = 0.1076$, goodness-of-fit on F^2: 0.815. R indices (all data) $R_1 = 0.0960$, w$R_2 = 0.1157$, largest diff. peak and hole: 0.416 and −0.311 e Å^{-3}.

Measurement computing and graphics: *SMART 1K CDD* (Bruker, 2000); cell refinement: *SMART*; data reduction *SAINT-Plus* (Bruker, 2000); programs(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELX97* (Sheldrick, 1997); molecular graphics: *SHELXTL97* (Sheldrick, 1997); software used to prepare material for publication: *SHELXTL97*.

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23. **General procedure for preparation of heterocyclic α-oxoacetic acid**. *Preparation of oxopyridin-3-ylacetic acid (**4b**).* A hydrochloric acid suspension (5 ml concentrated HCl plus 5 ml water) of (4-hydroxyphenylimino)pyridin-3-ylacetonitrile (**3b**) (450 mg; 2 mmol) was stirred at room temperature for 2 days. After approximately 1 h the reaction suspension becomes an orange solution, and overnight a yellow precipitate was formed. The reaction mixture was cooled at 0°C for a few hours. The solid, 4-aminophenol, was separated by filtration and water filtrate was evaporated at reduced pressure followed with azeotropic benzene (3×20 mL) drying of the solid residue. The solid residue contains a small amount of 4-aminophenol and the product, oxopyridin-3-ylacetic acid (**4b**). The solid was heated in methanol (10 ml) with stirring at 40°C for 15 min, the resulting suspension was cooled in ice-water bath, separated by filtration and dried at 80°C for 0.5 h to afford 210 mg (70%) of product. ^{1}H NMR (DMSO-d_6) δ 9.144 (1H, d, $J = 2.1$ Hz, pyridine 2-H), 8.907 (1H, dd, $J_1 = 5.4$ Hz, $J_2 = 2.1$ Hz, pyridine 6-H), 8.535 (1H, dt, $J_1 = 7.8$ Hz, $J_2 = 2.1$ Hz, pyridine 4-H), 7.790 (1H, dd, $J_1 = 7.8$ Hz, $J_2 = 5.4$ Hz, pyridine 5-H); ^{13}C NMR (DMSO-d_6) δ 161.633, 146.560, 143.869, 136.855, 124.432, 121.692, and 96.019 ppm. Anal. calcd for $C_7H_5NO_3$: C, 55.63; H, 3.33; N, 9.27. Found: C, 55.79; H, 3.55; N, 9.41%.