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Cyanide-Catalyzed Cyclizations via Aldimine Coupling

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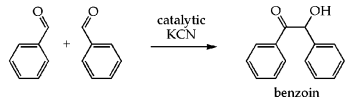
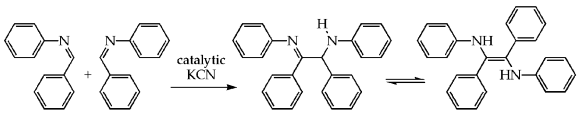
Abstract: Aldimine coupling (AIC) is the nitrogen analogue of the benzoin condensation and has been applied to dialdimines, providing the first examples of cyclizations effected by cyanide-catalyzed AIC. Sodium cyanide promoted the facile, intramolecular cyclization of several dialdimines in *N*,*N*-dimethylformamide, methanol, or methylene chloride/water (phase-transfer conditions) yielding a variety of six-membered heterocycles. Under aerobic conditions, an oxidative cyclization occurs to provide the diimine heterocycle. Oligomerization was observed with rigid dialdimines for which cyclization was precluded.

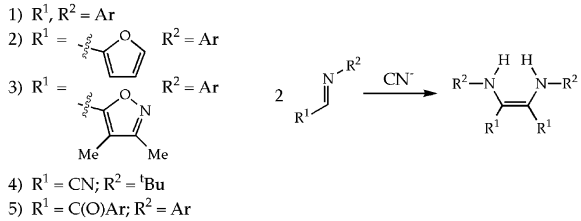
The cyanide-catalyzed benzoin condensation (eq 1) was first reported in 1824 by Stange[1] and has since been the subject of a large number of investigations.[2] For example, a detailed mechanism—attributable to Lapworth[3]—has been substantiated, and several competent catalysts have been identified.[4] The corresponding aldimine variation (eq 2) of this reaction was recognized in 1928 by Strain.[5] Subsequent reports related to this aldimine reaction have been scattered and provide comparatively little information on substrate variability, mechanism, and reaction scope.[6] The examples reported in the literature[7] are exclusively limited to simple dimerizations (eq 3) and fall into five general substrate classifications: aryl aldimines; furyl aldimines; isoxazole aldimines; cyano aldimines; and keto aldimines.



(1)



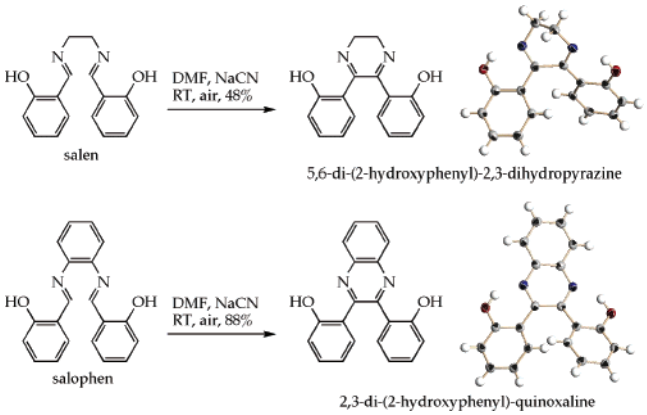
(2)



(3)

While further investigating the scope and generality of the aldimine dimerization reaction, we discovered the first examples of applying this aldimine coupling (AIC) reaction[8] to the *cyclization of difunctional substrates*. Our initial experiments involved the cyanide-catalyzed cyclization of the well-known salen ligand and its phenylene derivative (Scheme 1). To our knowledge, these represent

SCHEME 1. Pyrazine and Quinoxaline Heterocycles Prepared by a Novel Ring Closing Aldimine Coupling Reaction (Thermal Ellipsoids Are Shown with 50% Probability)



the first known examples of ring-closing aldimine coupling.[9] Complete characterization of the heterocycles 5,6-

* To whom correspondence should be addressed.

(1) Stange *Buch. Rep. Pharm.* **1824**, *16* (No. 93).

(2) (a) Ide, W. S.; Buck, J. S. *Org. React.* **1948**, *4*, 269−304. (b) Lachman, A. *J. Am. Chem. Soc.* **1924**, *46*, 708−723.

(3) (a) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995−1005. (b) Lapworth, A. *J. Chem. Soc.* **1904**, *85*, 1206−1213. (c) Kuebrich, J. P.; Schowen, R. L.; Wang, M.; Lupes, M. *J. Am. Chem. Soc.* **1971**, *93*, 1214−1220.

(4) Most alternatives to cyanide are thiazole derivatives. For example, 3,4,5-trimethylthiazolium iodide: (a) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 699−702. Thiamine: (b) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726.

(5) Strain, H. H. *J. Am. Chem. Soc.* **1928**, *50*, 2218−2223.

(6) (a) Strain, H. H. *J. Am. Chem. Soc.* **1929**, *51*, 269−273. The dehydrogenative pinacol-type coupling of aromatic aldimines can be effected with stoichiometric ytterbium metal and an oxidant: (b) Jin, W.-S.; Makioka, Y.; Taniguchi, Y.; Kitamura, T.; Fujiwara, Y. *Chem. Commun.* **1998**, *10*, 1101−1102. (c) Jin, W.-S.; Makioka, Y.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2001**, *66*, 514−520.

(7) (a) Aryl aldimine example: Becker, H.-D. *J. Org. Chem.* **1970**, *35*, 2099−2102. (b) Furyl aldimine example: Cariou, M.; Carlier, R.; Simonet, J. *Bull. Soc. Chim. Fr.* **1986**, *5*, 781−792. (c) Isoxazole example: Walia, J. S.; Guillot, L.; Singh, J.; Chattha, M. S.; Satyanarayana, M. *J. Org. Chem.* **1972**, *37*, 135−137. (d) Cyano aldimine example: Ferris, J. P.; Donner, D. B.; Lotz, W. *J. Am. Chem. Soc.* **1972**, *94*, 6968−6974. (e) Keto aldimine example: McKay, W. R.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, *9*, 2443−2450.

(8) The benzoin condensation is technically a dimerization since the molecular weight of benzoin is twice that of benzaldehyde. Hence, the term "coupling" is introduced to avoid the misleading descriptor "condensation", and is meant to apply generally to intermolecular and intramolecular reactions.

(9) For recent examples of intramolecular benzoin condensations (dialdehyde substrates) see: Modler-Spreitzer, A.; Fritsch, R.; Mannschreck, A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 555−560. Yang, Z.; Wong, H. N. C.; Hon, P. M.; Chang, H. M.; Lee, C. M. *J. Org. Chem.* **1992**, *57*, 4033−4034. Intramolecular cyclization of aldehyde−ketone substrates has recently been reported: Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432−8433.

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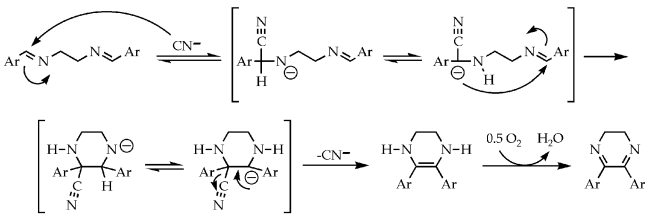
SCHEME 2. Proposed Mechanism for the Cyanide-Catalyzed Cyclization of Salen

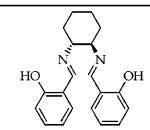
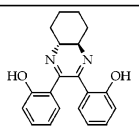
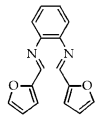
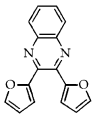
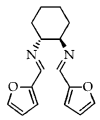
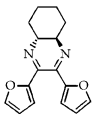
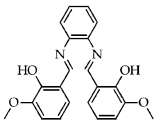
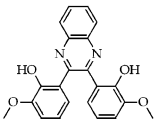
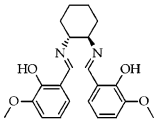
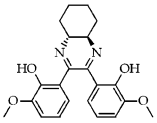
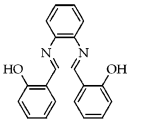
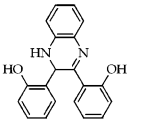
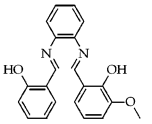
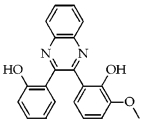
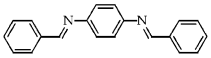


di(2-hydroxyphenyl)-2,3-dihydro-pyrazine[10] and 2,3-di(2-hydroxyphenyl)quinoxaline[11] confirmed the novel cyclization event and the subsequent oxidation to the diimine. Scheme 2 depicts the proposed mechanism for the cyclization of salen.

A number of additional dialdimines have been subjected to catalytic amounts of sodium cyanide. Table 1 reports a variety of observed cyclizations. Effective solvents include methanol and *N*,*N*-dimethylformamide, in which sodium cyanide is readily soluble. The choice of solvent, reaction temperature, and reaction duration are partially optimized according to the substrate employed.[12] While the reactions are clearly catalytic in sodium cyanide (e.g., salophen can be quantitatively cyclized with 10 mol % of NaCN; see the Supporting Information), high catalyst loadings (up to 100 mol %) expedite the reactions, yet do not greatly impact the cost or complicate the workup procedure.[13] It should be noted that three of the pyrazine and quinoxaline products are known and that their syntheses rely on the double Schiff base condensation of the corresponding diamine and diketone.[14] A disadvantage of this existing method is that oxygen is not used as the oxidant; harsher oxidants are typically employed to oxidize an α-hydroxy ketone to the diketone.

Entry 1 (Table 1) and the reactions from Scheme 1 demonstrate the ring closure of substrates derived from salicylaldehyde. The products are particularly stable due to the intramolecular hydrogen bonding (Scheme 1,

TABLE 1. Cyanide-Catalyzed Cyclizations of Dialdimines[a]

entry	substrate	product	solvent	yield (%)[c]
1			DMF	88
2			DMF	53
3			DMF	27
4			DMF	65
5			MeOH	41
6			CH_2Cl_2 H_2O Bu_4NI	56
7			MeOH	66
8		oligomers	MeOH	42

[a] Typical conditions: catalyst loading, 40−100 mol % of NaCN; room temperature to 65 °C; 24−48 h. See the Supporting Information. [c] Isolated yield.

N···H distances of 1.86, 1.83, 1.79, and 1.83 Å) and the presence of the OH group is significant since the corresponding cyclization of *N*,*N*′-dibenzylidene−ethane−1,2-diamine proceeds with poor yield under similar reaction conditions. However, intramolecular hydrogen bonding is certainly not necessary, as evidenced by the facile cyclization of substrates derived from furfural (entries 2 and 3). Interestingly, vanillin and related aldehydes are reported *not* to undergo the benzoin condensation under a variety of conditions.[15] In contrast, our attempts to cyclize dialdimines based on *o*-vanillin proceed well (entries 4 and 5). Phase-transfer conditions (entry 6) allow for the synthesis of a cyclized—yet unoxidized—heterocycle, which adopts the imine−amine tautomer shown because intramolecular hydrogen bonding is possible.[16] Entry 7 demonstrates the viability of cyclizing an unsymmetrical dialdimine to yield an unsymmetrical quinoxaline. Finally, rigid dialdimines, such as that in

(10) Orange-red blocks were grown by slow evaporation of an ethyl acetate solution. Crystal data: triclinic, *P*1, a = 5.8600(7) Å, b = 8.4944(10) Å, c = 13.4511(17) Å, α = 101.721(2)°, β = 98.011(2)°, γ = 99.562(2)°, V = 636.01(13) Å^3, Z = 2, T =110(2) K, R_1(on F_0) = 0.0602, wR_2(on F_0^2) = 0.1569, GOF = 1.089 for 184 parameters and 2189 unique data.

(11) Yellow plates were grown by slow evaporation of an acetone solution. Crystal data: triclinic, *P*1, a = 5.9430(9) Å, b = 8.6856(13) Å, c = 14.988(2) Å, α = 74.255(2)°, β = 81.050(2)°, γ = 83.614(2)°, V = 733.64(19) Å^3, Z = 2, T =110(2) K, R_1(on F_0) = 0.0572, wR_2(on F_0^2) = 0.1430, GOF = 1.091 for 225 parameters and 2472 unique data.

(12) A typical cyclization (salophen, Scheme 1): A 500-mL round-bottom flask was charged with 8.00 g (25.3 mmol) of *N*,*N*′-bis-(salicylidene)-*o*-phenylenediamine, 0.496 g (10.1 mmol) of NaCN, and 110 mL of *N*,*N*-dimethylformamide. This mixture was allowed to stir for 48 h and then poured into ice water. The precipitated solid was isolated by filtration, dissolved in methylene chloride, and dried with $MgSO_4$. Filtration and in vacuo drying afforded 7.00 g (87.5%) of the product as a yellow powder. See the Supporting Information for full synthetic details.

(13) Extreme caution should always be taken when handling any form of cyanide. All reactions should be conducted in a well-ventilated fume hood and one should avoid the addition of acid during workup as this evolves HCN. The products reported herein were conveniently isolated by filtration as crystalline solids from which NaCN readily washed away.

(14) Quinoxaline from Scheme 2: (a) Tanaka, S.; Yokoyama, K.; Takashima, M. Japanese Patent 40,012,294, 1965. Quinoxaline from entry 2: (b) Bost, R. W.; Towell, E. E. *J. Am. Chem. Soc.* **1948**, *70*, 903−905. Pyrazine from entry 3: (c) Jimeno, M. L.; de Paz, J. L. G.; Rodriguez, J.; Rodriguez, M.; Ochoa, C. *Anal. Quim.* **1994**, *90* (7−8), 423−431.

(15) Pearl, I. A. *J. Am. Chem. Soc.* **1952**, *74*, 4620−4662.

(16) An X-ray crystallographic study (see the Supporting Information) clearly shows the imine−amine tautomer of the heterocycle from entry 6—not the alternative ene−diamine tautomer described in eq 2. The imine−amine tautomer is stabilized by a single intramolecular hydrogen bond in the solid state (N···H = 1.35 Å).

entry 8, are precluded from intramolecular cyclizations. Instead, they undergo oligomerization via a step growth mechanism.[17]

In conclusion, we have demonstrated the first cyanide-catalyzed cyclizations through aldimine coupling (AIC). Under normal aerobic conditions, an oxidative cyclization occurs to provide the diimine heterocycle; however, phase-transfer conditions can select for an unoxidized heterocycle bearing the imine−amine functionality. Sodium cyanide, a very inexpensive catalyst, is capable of promoting this reaction and, for the first time, has been found competent for (1) coupling aldimines based on *o*-vanillin, (2) coupling aldimines under phase-transfer conditions, (3) cyclizing unsymmetrical dialdimines to prepare unsymmetrical heterocycles, and (4) coupling aldimines to yield conjugated oligomers. The AIC reaction appears to be an underutilized, yet simple and powerful carbon−carbon bond-forming reaction. It is envisioned that this reaction will be widely applicable to dimerization, cyclization, and polymerization reactions that employ common aldehydes and amines as synthons. The cyclized products are generally highly colored, extensively conjugated, and fluorescent; thus, we have an interest in exploring their properties as organic dyes and as organometallic dyes upon coordination of metals. Other current targets include novel heterocycles, macrocycles, chiral ligands for homogeneous catalysis, liquid crystals, and conjugated as well as nonconjugated polymers.

(17) ^{1}H NMR end-group analysis indicates an average degree of polymerization of 4.34. While the monomer is colorless, the oligomeric product exhibits an orange-red coloration indicative of a long, conjugated system.

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Supporting Information Available: Experimental procedures and compound characterization data, including X-ray crystallographic data for 5,6-di(2-hydroxyphenyl)-2,3-dihydropyrazine and 2,3-di(2-hydroxyphenyl)quinoxaline. This material is available free of charge via the Internet at http://pubs.acs.org.

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