The Wolff-Kishner Reduction of 2-Acetonyl Pyrazines and Pyridines. A Novel Rearrangement

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Wolff-Kishner reduction of 1-(6-methylpyrazin-2-yl)-2-propanone leads to the formation of 2-isopropyl-6-methylpyrazine (**2a**), in addition to the expected 6-methyl-2-*n*-propylpyrazine. The by-product **2a** is suggested to arise *via* a spirocyclopropylidene aza-anion, which serves as a conduit between the initial less-stable secondary 1-(2-pyrazinyl)-2-propyl carbanion and the more stable primary 2-(2-pyrazinyl)-1-propyl carbanion. Similar results were observed for the 1-(3-methylpyrazin-2-yl) and 1-(6-methylpyridin-2-yl)-2-propanones. The extent of by-product formation diminished in the pyridine ring system. Electrophilic activation of the ring appears essential since the benzene analog phenylacetone gave no detectable cumene under identical reaction conditions.

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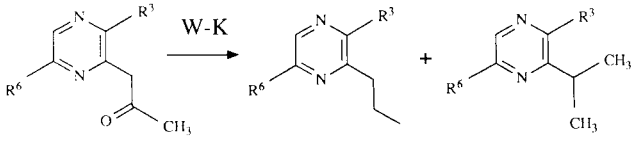
One of the most fascinating if not frustrating aspects of synthetic organic chemistry is the observation of unexpected products in what might otherwise have been predicted to be a simple extension of a well known and established preparative reaction. The recent report [1] of Otterbach and Musso on the Wolff-Kishner induced ring cleavage of a tricyclic ketone encourages our report of a skeletal rearrangement of various pyrazinyl acetones **1** to related isopropyl pyrazines **2** (Scheme I) in the course of a Wolff-Kishner reduction.

Scheme I



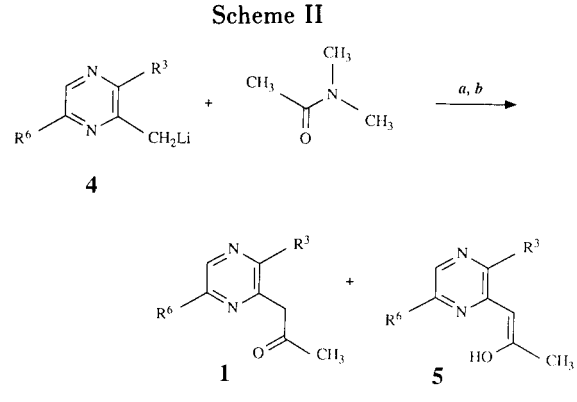
1 **3** **2**

Series a: R^3 = H, R^6 = Me

Series b: R^3 = Me, R^6 = H

In the course of our studies of the conformational analysis of aromatic and heteroaromatic molecules by supersonic molecular jet spectroscopy [2], we required the preparation of 2-methyl-6-*n*-propylpyrazine (**3a**). When the reaction between 6-methyl-2-pyrazinylmethyllithium (**4a**) and iodoethane was found to be of low yield and accompanied by the formation of numerous tediously removed by-products, an alternative method depicted in Schemes I and II was examined. The reaction of **4a** with *N,N*-dimethylacetamide in anhydrous diethyl ether, followed by aqueous workup, led to useful quantities (31%) of 2-methyl-6-(2-oxopropyl)pyrazine (**1a**) [which exists, at least in deuteriochloroform, in equilibrium with its tautomer, 2-methyl-6-(*E*-2-hydroxy-1-propen-1-yl)pyrazine (**5a**)]. When subjected to the Huang-Minlon variation of the Wolff-Kishner reduction, ketone **1a** afforded deoxygenated pyrazine products nearly quantitatively. Unexpectedly, nearly 16% of the product proved to be 2-methyl-6-isopropylpyrazine (**2a**) instead of **3a**.

Scheme II



Series a: R^3 = H, R^6 = Me

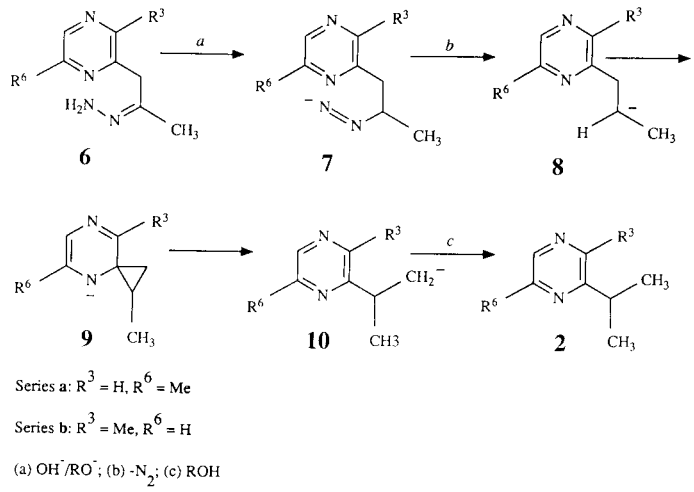
Series b: R^3 = Me, R^6 = H

(a) Et_2O; (b) H_2O

A likely explanation for this novel rearrangement is shown in Scheme III. Evidently the inferred carbanion **8**, generated by the expulsion of dinitrogen from the diimide-anion **7**, is not entirely quenched by the hydroxylic protons in the medium. Able to compete is a cyclization involving the addition of the *secondary* carbanion into the adjacent electrophilic C=N bond to generate a methyl-substituted spirocyclopropyl intermediate such as **9**. This intermediate (or transition-state) can then collapse, regenerating the aromatic pyrazine ring, along with the more stable *primary* carbanion **10**, whose protonation-quenching would yield the observed by-product **2a**.

This reaction sequence was also explored, starting with 2,3-dimethylpyrazine (**11**) (Schemes I-III, series b). The adjacent methyl-substituent did not provide enough steric hindrance to significantly alter the outcome of the reac-

Scheme III



Series a: R^3 = H, R^6 = Me

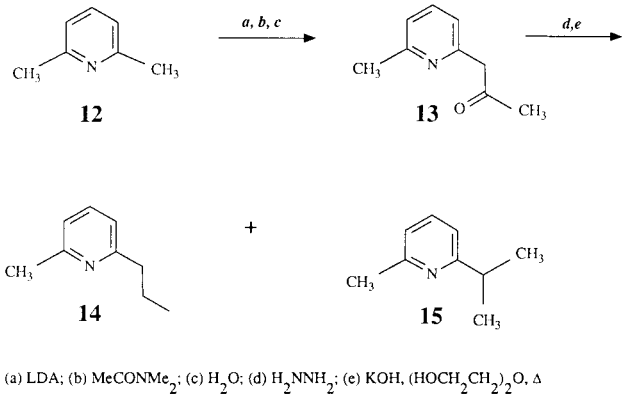
Series b: R^3 = Me, R^6 = H

(a) OH^-/RO^-; (b) $-N_2$; (c) ROH

tion: isopropyl-substituted by-product **2b** was observed in similar amount (*circa* 19% by glc). Cleavage of intermediates to regenerate **11** occurred to the extent of 6%.

2,6-Lutidine (2,6-dimethylpyridine, **12**) was subjected to similar chemistry. As expected, given the less electron-deficient nature of a pyridine relative to a pyrazine, the extent of rearrangement was diminished, but was still as much as 4.5% (by glc) (Scheme IV).

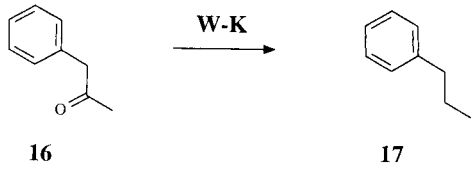
Scheme IV



(a) LDA; (b) $MeCONMe_2$; (c) H_2O; (d) H_2NNH_2; (e) KOH, $(HOCH_2CH_2)_2O$, Δ

Under similar conditions, phenylacetone (**16**) afforded *n*-propylbenzene (**17**) (Scheme V) without any detectable formation of cumene, further suggesting a need for internal activation of the aromatic ring system to allow intramolecular nucleophilic attack by the intermediary carbanion.

Scheme V



In all cases, total recovery of well-defined products was high (>95%), showing that the reactions were clean, except for the observed rearrangement and lesser "Retro-Claisen" style cleavage, which regenerated a few mole per cent of the methylpyrazine precursor. The two principal products were readily separated by chromatographic methods. The isopropyl derivative was more volatile and less polar than the *n*-propyl analog in all cases. This is not surprising, given our recent conformational studies [2] of alkylbenzenes and alkylheteroaromatics. The preferred conformation of an isopropyl group is with the C-H bond lying in the plane of the ring, with the two methyl groups lying equally disposed above and below, providing a modicum of steric hindrance to associative intermolecular pi-pi interaction with *either* side of the ring.

We note other reports [1,4] of rearrangement or fragmentation under Wolff-Kishner conditions, in particular that of tricyclo[4.2.1.$1^{2,5}$]dec-3-en-9-one [1]. These reports are further evidence for a finite lifetime for the carbanionic intermediates, such that novel and unexpected chemistry can sometimes intrude.

EXPERIMENTAL

Starting materials were obtained from Aldrich or Pyrazine Specialties, Inc., and employed without further purification. Solvents were obtained routinely and employed without further purification. The nmr spectra were determined on a Varian XL-300 or XL-400 instrument. Analyses glc were determined with a Varian 3400 Gas Chromatograph and glc/ms with a Finnegan 3300 with INCOS-IV Data System. A Chromatotron® (Model 7924) is the centrifugal thin layer chromatographic system developed by Harrison Research, Inc. Steam distillation as employed here consisted of a simple co-distillation with water.

1-(6-Methyl-2-pyrazinyl)-2-propanone (**1a**) [3].

A stirred solution of 2,6-dimethylpyrazine (10.86 g, 0.1 mole) and diisopropylamine (10 ml, 0.07 mole) in diethyl ether (291 g) at

0° was treated over 8 minutes with *n*-butyllithium (43 ml, 2.5 *M* in hexanes, 0.11 mole) from a syringe; dark red granular solids (6-methyl-2-pyrazinylmethyllithium, **4a**) separated. The resulting slurry was cooled to −78°, and treated as rapidly as possible (*ca.* 30 seconds) with a solution of *N,N*-dimethylacetamide (12 ml, 0.13 mole) in diethyl ether (60 ml). The resulting mixture was allowed to warm to room temperature with stirring to complete the reaction. The reaction mixture was quenched with water (100 ml). A deep yellow color formed at once and the mixture soon deposited a yellow solid (the lithium salt of the enolate of the desired product). The solid was vacuum filtered and rinsed with a minimal volume of ether. The aqueous phase was back-extracted once with ether, mildly acidified with glacial acetic acid (10 ml), and extracted with 100 ml portions (4x) of ethyl acetate until uv-active material was no longer recovered. The recovered solid, including that adhering to the reaction vessel, was treated separately. It was dissolved in water (100 ml), acidified with acetic acid (4 ml), and similarly extracted with ethyl acetate. The two sets of extracts were processed separately by evaporation *in vacuo*, and Kugelrohr distillation. The appropriate fractions (7.75 g) were combined and chromatographed [Silica Gel 60, 131 g, using 20% (v/v) acetone in hexane], eluting as a bright yellow band. The principal impurity, *N,N*-dimethylacetoacetamide, was retained by the column. The single component fractions were combined, concentrated *in vacuo*, and Kugelrohr distilled [bp 62-68° (external)/0.245-0.500 Torr], yield 5.16 g (34%); ^{1}H nmr (deuteriochloroform): δ keto form 2.28 (3H, s), 2.56 (3H, s), 3.94 (2H, s), 8.31 (H, s), 8.37 (H,s); enol form 2.06 (3H, s), 2.48 (3H, s), 5.37 (H, d, J = 0.7 Hz), 8.08 (H, s), 8.09 (H, s), enol OH not observed; ^{13}C nmr (deuteriochloroform at 77.42): δ keto form 203.92 (C=O), 153.01 (2), 149.10 (6), 142.38 and 141.99 (3,5), 49.82 (CH_2), 30.09 (CH_3CO), 21.36 (6-CH_3); enol form 166.88 (C=COH), 152.76, 148.50, 139.43, 138.23, 93.25 (C=COH), 21.90, 20.83. The enol content appeared to amount to 8-10% of the total; glc/ms: m/z 150 (Observed = Calcd. for $C_8H_{10}N_2O$).

2-Methyl-6-*n*-propylpyrazine (**3a**).

1-(6-Methyl-2-pyrazinyl)-2-propanone (**1a**) (2.01 g, 13.38 mmoles) was dissolved in methanol (*ca.* 20 ml) and treated with excess 95% hydrazine (2 ml) at room temperature. After standing overnight under nitrogen, the mixture was concentrated *in vacuo* at 40°. Diethylene glycol (53 ml) was added, and rinsed in with water (10 ml). A solution of potassium hydroxide (2.29 g) in water (10 ml) was added, and the mixture heated to boiling. Gas evolution (nitrogen) began after most of the water had distilled. Heating was continued until gas evolution ceased. Water (50 ml) was added to the hot reaction mixture, and the product steam distilled. The product initially formed a second phase, but dissolved as the aqueous distillate increased in volume. Dichloromethane was distilled through the apparatus at the end to rinse the condenser, extract the product, and help protect it from evaporation pending further workup. Evaporation of the resulting extracts *in vacuo* afforded 1.75 g (96% recovery) of crude product. This material contained about 16% 2-methyl-6-isopropylpyrazine (**2a**) by glc, in addition to some regenerated 2,6-dimethylpyrazine, and needed repeated use of the Chromatotron® [5% acetone (v/v) in hexane/silica gel] to obtain pure product. The purified material was identical to that isolated by an equally laborious workup from a reaction of 6-methyl-2-pyrazinylmethyllithium (**4a**) with iodoethane [2]; ^{1}H nmr (deuteriochloroform): δ 0.99 (3H, t, J = 7.4 Hz), 1.76 (2H, sextet, J = 7.5 Hz), 2.54 (3H, s), 2.75 (2H, t, J = 7.7 Hz), 8.25 (H, s), 8.28 (H, s); ^{13}C nmr (deuteriochloroform at 76.92): δ 156.21 (2), 152.60 (6), 141.48 (3), 140.96 (5), 37.48 ($CH_2CH_2CH_3$), 22.96 ($CH_2CH_2CH_3$), 21.54 (2-CH_3), 13.79 ($CH_2CH_2CH_3$).

2-Methyl-6-(1-methylethyl)pyrazine (**2a**).

Enough was isolated from the Chromatotron® separation to allow nmr analysis; ^{1}H nmr (deuteriochloroform): δ 1.33 (6H, d, J = 7 Hz), 2.54 (3H, s), 3.07 (H, septet, J = 7 Hz), 8.28 (H, s), 8.29 (H, s). This data is identical to that from material obtained from the reaction of 2-methylpyrazine with acetone and sodium metal [5]; ^{13}C nmr (deuteriochloroform at 77.11): δ 161.25 (6), 152.70 (2), 141.85 (3), 139.60 (5), 34.14 (Me_2CH), 22.24 (2C, Me_2CH), 21.61 (2-CH_3). Corresponding chemical shifts for the alternatively synthesized [5] material are 161.45, 152.93, 142.07, 139.81, 34.35, 22.47, 21.82 (deuteriochloroform at 77.43). The gc retention times and glc/ms data for both samples were identical.

REFERENCES AND NOTES

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[3] A. C. Tas and R. J. C. Kleipool, *Reichst. Aromen, Koerperpflegem*, **24**, 326,328,331 (1974); *Chem. Abstr.*, **82**, 57645m (1975).

[4] R. P. Lemieux and P. Beak, *Tetrahedron Letters*, **30**, 1353 (1989) and references cited therein.

[5] A. F. Bramwell, L. S. Payne, G. Riezebos, P. Ward and R. D. Wells, *J. Chem. Soc. (C)*, 1627 (1971).