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FRIEDLÄNDER REACTIONS OF TRIACETYLMETHANE – UNUSUAL DISTRIBUTION OF PRODUCTS -

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Abstract – Friedländer reactions of triacetylmethane with selected β-amino-α,β-unsaturated aldehydes afforded pyridoheterocycles and their 2-methyl derivatives instead of triheteroarylmethane.

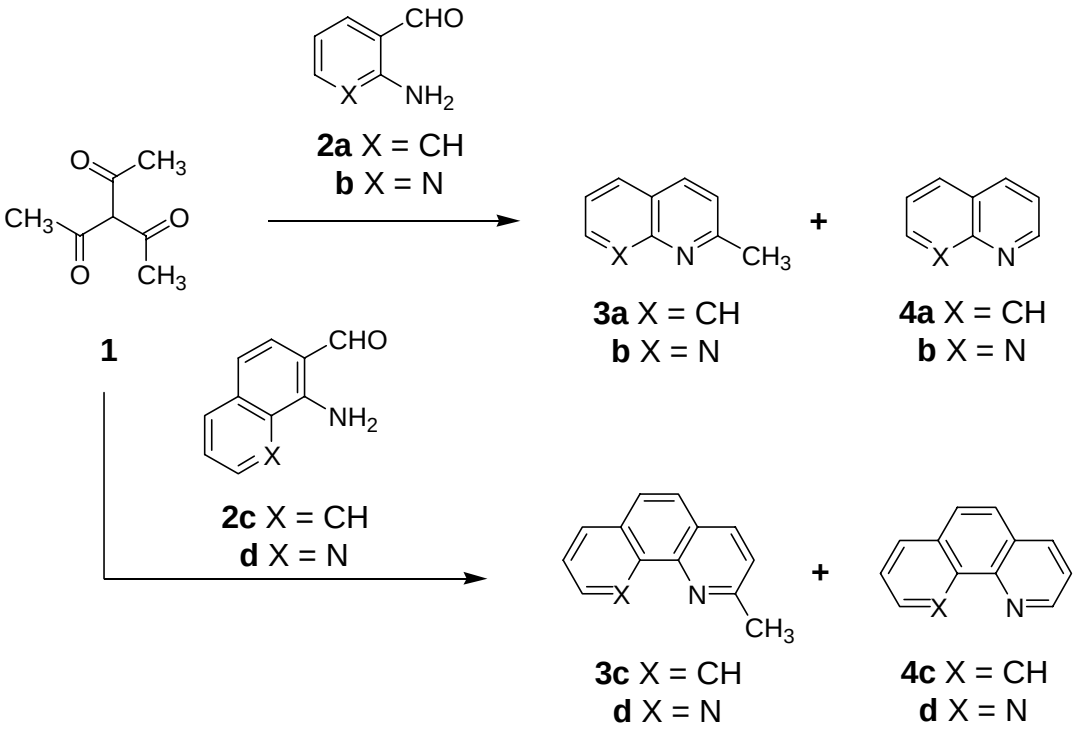
INTRODUCTION

The Friedländer condensation, a reaction of β-amino-α,β-unsaturated aldehydes or *o*-aminophenones with enolizable ketones with the loss of two molecules of water, has been one of the facile and efficient methods to construct quinoline and related nuclei in a variety of intriguing molecules.[1] A variety of β-amino-α,β-unsaturated aldehydes were introduced as synthons for the Friedländer reaction and contributed to expand the scope of the reaction in heterocyclic chemistry, which were recently reviewed.[2] As a part of our interests in new polydentates and their metal complex chemistry, we have involved in the synthesis of tris(heteroar-2-yl)methane. We herein described unusual product distribution of Friedländer reaction of triacetylmethane with selected β-amino-α,β-unsaturated aldehydes.

RESULTS AND DISCUSSION

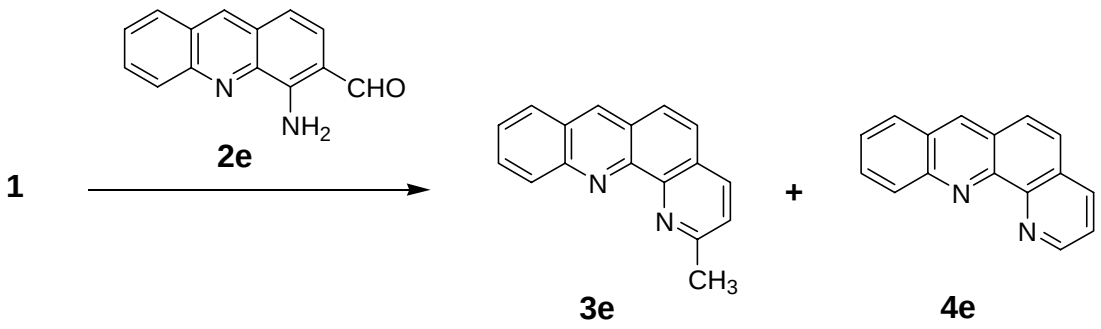
To the best of our knowledge, Friedländer reaction of **1** has never been attempted while reactions of related 2,4-pentanedione have been extensively studied with a variety of *o*-aminoarene aldehydes.[3] Reaction of triacetylmethane (**1**) with 2-aminobenzaldehyde (**2a**)[4] under general Friedländer condition, refluxing in EtOH with catalytic amount of KOH, afforded 2-methylquinoline (**3a**) and quinoline (**4a**) in a ratio of 3:1 instead of expected 3-(quinolin-2-yl)-2,4-pentanedione and/or tri(quinolin-2-yl)methane (Scheme 1). For comparison, reaction of **2a** with 1.2 equivalents of **1** was examined to provide similar result. From the reaction with 2-aminonicotinaldehyde (**2b**),[5] 2-methyl-1,8-naphthyridine (**3b**)[6] was

obtained as a major product (58%) with a trace amount (3.8%) of 1,8-naphthyridine (**4b**).[7] Similarly, reactions with 1-aminonaphthalene-2-carbaldehyde (**2c**)[8] and 8-aminoquinoline-7-carbaldehyde (**2d**)[8] gave corresponding benzo- and pyrido-fused 2-methylquinolines (**3c**,**d**)[9,10] and their demethylated derivatives (**4c**,**d**),[11,12] respectively. The ratios of **3c**,**d** and **4c**,**d** were 1.4:1 to 1.8:1 with 72% and 77% yield, respectively, based on triacetylmethane employed.



Scheme 1

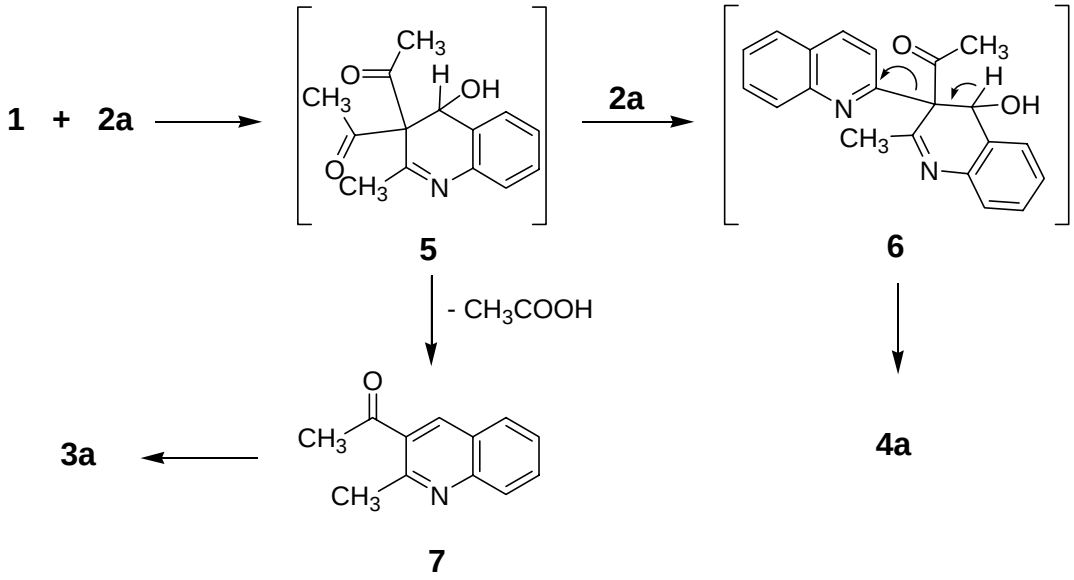
The generality of the reaction was examined with 4-aminoacridine-3-carbaldehyde (**2e**)[13] to afford corresponding 2-methylbenzo[*b*]-1,10-phenanthroline (**3e**) and benzo[*b*]-1,10-phenanthroline (**4e**)[14] in 82% yield with a ratio of 1.7:1 (Scheme 2). The products could be readily characterized by their ^{1}H NMR spectra. Even it is not able to completely resolve and assign all the proton resonances, certain features were characteristic and diagnostic. Typically, H2 of **4e** was resonanced at δ 8.59 with characteristic pyridine coupling constants ($J_{H2,H3}$ = 4.4 Hz and $J_{H2,H4}$ = 1.5 Hz). H11's of **3e** and **4e** are experiencing deshielding effect of the lone pairs of electrons on neighboring nitrogen, thus shifted down-field to δ 8.59 and δ 8.65, respectively. Resonances of remaining protons were assigned by double-quantum filtered COSY experiments and NOE effect for the selected protons.



Scheme 2

To get information for the reaction mechanism, we stopped the reaction of **1** with **2a** at the intermediate stage by quenching after 2 h reflux (Scheme 3). Thus the intermediate was isolated and identified as 3-methyl-2-acetylquinoline (**7**)[3a] in 90% yield with a trace of dimeric species of **2a** (<5%). Process for the formation of **7** may include an intermediate (**5**), which can be formed by employing more acidic methine hydrogen instead of terminal methyl hydrogen. Similar pattern of reaction was previously observed when 2,4-pentanedione was reacted with β-aminoacrolein,[15] **2a**,[3a] and **2b**[3b] to afford 2-methyl-3-acetylpyridine, **7**, and 2-methyl-3-acetyl-1,8-naphthyridine, respectively.

On the basis of these observations, we believe that formation of **3a**, thus, can be explained by base-catalyzed deacetylation[16] of **7** and/or aromatization, followed by base-catalyzed deacetylation of doubly condensed intermediate (**6**). To support proposed mechanism, deacetylation of isolated **7** was examined. The desired **3a** was obtained in 85% yield when isolated 2-methyl-3-acetylquinoline (**7**) was subjected to the original reaction conditions. On the other hand, aromatization of **6** might generate demethylated product (**4a**) with as yet unidentified product.



Scheme 3

In conclusion, Friedländer reactions of triacetylmethane with selected *o*-aminoarene aldehydes afforded a series of pyridofused compounds and their 2-methyl derivatives, respectively, instead of expected tri(heteroar-2-yl)methane. The reaction may proceed *via* 2-methyl-3-acetylquinoline.

EXPERIMENTAL

Melting points were determined using a Fischer-Jones melting points apparatus and are not corrected. IR spectra were obtained using a Perkin-Elmer 1330 spectrophotometer. NMR spectra were obtained using a Bruker-250 spectrometer 250 MHz or 400 MHz for ^{1}H NMR and 62.5 MHz or 100 MHz for ^{13}C NMR and are reported as parts per million (ppm) from the internal standard tetramethylsilane (TMS). Chemicals and solvents were commercial reagent grade and used without further purification. Elemental analyses were taken on a Hewlett-Packard Model 185B elemental analyzer.

Reaction of triacetylmethane (1) with 2-aminobenzaldehyde (2a)[17] (General Procedure)

A mixture of **1** (142 mg, 1.0 mmol) and 2-aminobenzaldehyde (397 mg, 3.3 mmol) in 10 mL of dry EtOH with saturated ethanolic KOH (1.3 mL, 0.2 mmol) was refluxed for 8 h. The solvent was evaporated under reduced pressure and resulting oily material was chromatographed on silica gel column eluting with CH_2Cl_2. The early fractions (R_f = 0.6, CH_2Cl_2) afforded 62 mg (48%) of 2-methylquinoline (**3a**) and the latter fractions (R_f = 0.35, CH_2Cl_2) afforded 20 mg (16%) of quinoline (**4a**). Physical and spectral data (IR, ^{1}H and ^{13}C NMR) for these compounds were identical to those reported previously in the literature.[18]

2-Methyl-1,8-naphthyridine (**3b**) Gray needles (58%): mp 114-115 ^{o}C (methylcyclohexane) (lit.,[6] mp 114-115 ^{o}C).

1,8-Naphthyridine (**4b**) Colorless glassy needles (3.8%): mp 97-98 ^{o}C (petroleum ether:CH_2Cl_2 = 1:1) (lit.,[7] mp 98 ^{o}C).

2-Methylbenzo[*h*]quinoline (**3c**) Pale yellow needles [42%, R_f = 0.6 (CH_2Cl_2)]: mp 47-48^{o}C (petroleum ether:CH_2Cl_2 = 1:1) (lit.,[9] bp 322-324 ^{o}C).

Benzo[*h*]quinoline (**4c**) White needles [33%, R_f = 0.4 (CH_2Cl_2)]: mp 51-52 ^{o}C (petroleum ether:CH_2Cl_2 = 1:1) (lit.,[11] mp 51-52 ^{o}C).

2-Methyl-1,10-phenanthroline (**3d**) White needles [39%, R_f = 0.2 (CH_2Cl_2)]: mp 51-52 ^{o}C (petroleum ether) (lit.,[10] mp 51-52 ^{o}C).

1,10-Phenanthroline (**4d**) White needles [33%, R_f = 0.05 (CH_2Cl_2)]: mp 116 ^{o}C (95% EtOH) (lit.,[12] mp 117 ^{o}C).

2-Methylbenzo[*b*]-1,10-phenanthroline (**3e**) White needles [52%, R_f = 0.50 (CH_2Cl_2:CH_3OH = 9:1)]: mp 58-60 ^{o}C (petroleum ether:CH_2Cl_2 = 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.71 (s, H7), 8.59 (dd, *J* =

8.4, 1.0 Hz, 1H, H11), 8.09 (d, *J* = 8.0 Hz, 1H, H4), 8.02 (dd, *J* = 8.4, 1.0 Hz, 1H, H8), 7.82 (ddd, *J* = 8.4, 7.5, 1.4 Hz, 1H, H10), 7.79 (d, *J* = 9.0 Hz, 1H, H5/H6), 7.63 (d, *J* = 9.0 Hz, 1H, H6/H5), 7.61 (ddd, *J* = 8.4, 7.5, 1.2 Hz, 1H, H9), 7.53 (d, *J* = 8.1 Hz, 1H, H3), 2.97 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 159.24, 148.26, 146.82, 146.21, 136.19, 135.76, 131.15, 129.78, 127.50, 127.30, 127.21, 126.89, 126.64, 126.03, 125.88, 124.11, 25.78. *Anal*. Calcd for $C_{17}H_{12}N_2 \bullet 0.5H_2O$: C, 80.61; H, 5.17; N, 11.06. Found: C, 80.29; H, 5.54; N, 11.05.

Benzo[*b*]-1,10-phenanthroline (**4e**) Pale yellow needles [30%, R_f = 0.20 (CH_2Cl_2: CH_3OH = 9:1)]: mp 113-114 °C (petroleum ether:CH_2Cl_2 = 1:1) (lit.,[14] mp 113 °C). Unreported spectral data are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (dd, *J* = 4.4, 1.5 Hz, 1H, H2), 8.72 (s, 1H, H7), 8.65 (d, *J* = 8.8 Hz, 1H, H11), 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H, H4), 8.03 (d, *J* = 8.8 Hz, 1H, H8), 7.86 (td, *J* = 8.8, 1.3 Hz, 1H, H10), 7.83 (d, *J* = 8.9 Hz, 1H, H5/H6), 7.66 (d, *J* = 9.2 Hz, 1H, H6/H5), 7.66 (t, *J* = 8.8 Hz, 1H, H9), 7.62 (dd, *J* = 8.0, 4.4 Hz, 1H, H3). ^{13}C NMR NMR (62.5 MHz, $CDCl_3$) δ 150.03, 148.44, 147.09, 146.94, 135.93, 135.74, 130.88, 130.15, 129.32, 127.61, 127.44, 127.09, 126.78, 126.74, 125.89, 123.56. *Anal*. Calcd for $C_{16}H_{10}N_2 \bullet 0.5H_2O$: C, 80.32; H, 4.63; N, 11.71. Found: C, 80.53; H, 4.65; N, 11.68.

2-Methyl-3-acetylquinoline (**7**) White needles: mp 78 °C (petroleum ether) (lit.,[3a] mp 74-75 °C). Unreported spectral data are as follows: ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.48 (s, 1H, H4), 8.03 (d, *J* = 8.4 Hz, 1H, H8), 7.85 (d, *J* = 8.1 Hz, 1H, H5), 7.78 (ddd, *J* = 8.5, 7.8, 1.5 Hz, 1H, H7), 7.54 (td, *J* = 8.0, 0.9 Hz, 1H, H6), 2.90 9s, 3H), 2.70 (s, 3H). ^{13}C NMR NMR (62.5 MHz, $CDCl_3$) δ 199.87, 157.63, 148.12, 138.31, 131.81, 131.12, 128.48, 128.34, 126.73, 125.62, 29.24, 25.57. MS, m/z (rel. intensity) 186.2 (100, M+1).

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