OZONOLYSIS OF TRI- AND TETRA-SUBSTITUTED FURANS TO α-DICARBONYL COMPOUNDS

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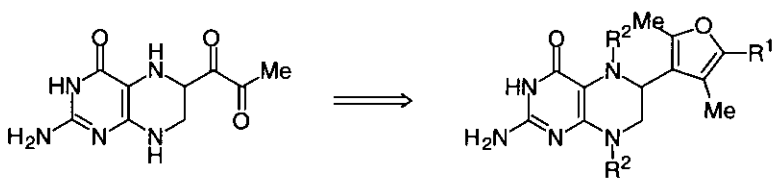
Abstract - This paper reports the oxidative conversion of 2,4,5-trimethylfur-3-yl and 2,4-dimethylfur-3-yl groups with ozone into pyruvoyl substituents.

Furan is readily susceptible to oxidative ring cleavage, and as a consequence a furyl substituent is often utilized as a latent carboxylic acid or carbonyl-containing substituent.[1] In pursuing our synthetic approach to 6-pyruvoyl-5,6,7,8-tetrahydropterin (**1**), considered to be a biogenetic precursor of the cofactor tetrahydrobiopterin,[2] we have devised a strategy involving oxidative degradation of an N^5, N^8-protected 5,6,7,8-tetrahydropterin carrying a 2,4,5-trimethylfuryl or a 2,4-dimethylfuryl substituent at C-6 (**2**). In a preliminary investigation of this concept, we describe herein the oxidation of a number of *N*-acyl-*N*-(1-furylethyl)anilines (**3**-**6**), which were considered to be reasonable models of **2**.

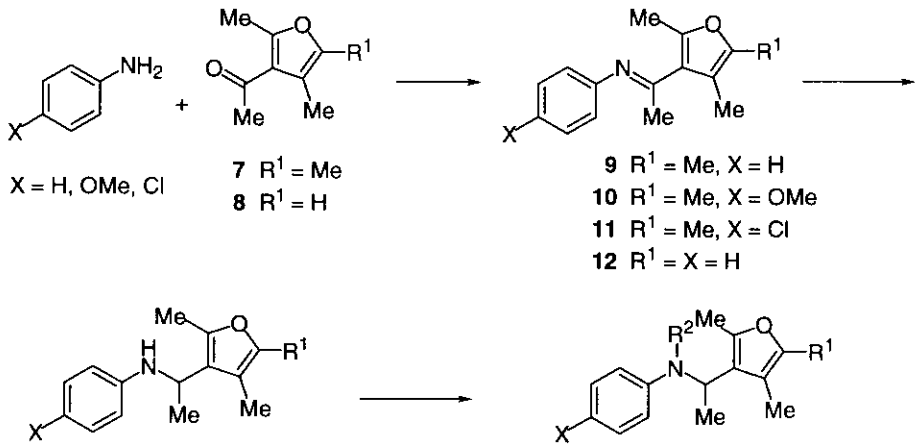


1 **2** R^1 = Me, H; R^2 = Protecting group

Model compounds (**3**-**6**) were prepared as outlined in Scheme 1. Zinc chloride-mediated cyclization of acetoin or hydroxyacetone with acetylacetone gave the 3-acetylfurans (**7**) and (**8**), respectively. The Schiff bases (**9**-**12**) were then obtained by *p*-toluenesulfonic acid-catalyzed condensation of **7** and **8** with anilines in the presence of 4Å molecular sieves. No imine was formed under these conditions with ketone (**7**) and 4-nitroaniline. Reduction of **9**-**12** with sodium borohydride or sodium cyanoborohydride proceeded readily to afford the amines (**13**-**16**), which were acetylated with acetic anhydride/4-dimethylaminopyridine (DMAP) in pyridine to furnish the *N*-acetylated oxidation precursors (**3a**-**6a**). Alternatively, the *N*-benzyloxycarbonyl derivatives (**3b**-**6b**) were formed by treatment of **13**-**16** with benzyl chloroformate in pyridine. Reaction of **9**-**12** with sodium

cyanoborohydride in the presence of benzyl chloroformate was not successful as an alternative procedure.

Scheme 1



X = H, OMe, Cl

7 R^1 = Me
8 R^1 = H

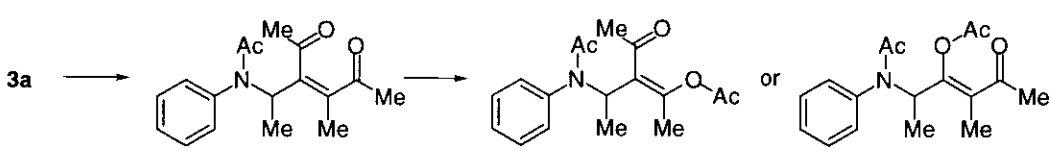
9 R^1 = Me, X = H
10 R^1 = Me, X = OMe
11 R^1 = Me, X = Cl
12 R^1 = X = H

13 R^1 = Me, X = H
14 R^1 = Me, X = OMe
15 R^1 = Me, X = Cl
16 R^1 = X = H

3a R^1 = Me, R^2 = Ac, X = H
3b R^1 = Me, R^2 = CO_2Bn, X = H
4a R^1 = Me, R^2 = Ac, X = OMe
4b R^1 = Me, R^2 = CO_2Bn, X = OMe
5a R^1 = Me, R^2 = Ac, X =Cl
5b R^1 = Me, R^2 = CO_2Bn, X = Cl
6a R^1 = X = H, R^2 = Ac
6b R^1 = X = H; R^2 = CO_2Bn

Reagents which are known to oxidize furans include 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[3] pyridinium chlorochromate (PCC),[4] or *m*-chloroperbenzoic acid (*m*-CPBA).[5] Use of either of the former two reagents for the oxidation of **3a**, however, did not lead to detectable amounts of the enedione (**17**), although the substrate was completely consumed in both cases. Treatment of **3a** with 2 equivalents of *m*-CPBA below 0 °C gave an oil which was identified as **18** (or its isomer **19**), as judged by elementary analysis and ^{13}C NMR spectroscopy (3 carbonyl peaks at δ 201, 170 and 169 ppm). Formation of the esters (**18**) or (**19**) may be rationalized as the result of a Baeyer-Villiger oxidation of the initially formed dicarbonyl compound (**17**).[6] Use of a lesser amount of *m*-CPBA gave several oxidation products containing **18** (or **19**) along with some recovered starting material.

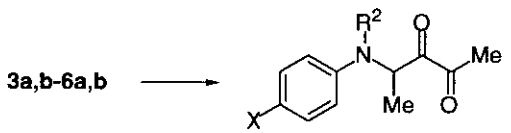
Scheme 2



17 **18** **19**

Ozonolysis of 2,5-diphenylfuran has been shown to give phenylglyoxal as a result of initial oxidation to the enedione followed by cleavage of the double bond.[7] Oxidation of the carbamate (**6b**) with 2 equivalents of ozone in dichloromethane at -78 °C successfully produced the pyruvoyl compound (**20b**) in 16% yield, together with 5% of recovered **6b**. Attempted oxidation of **3b** under the same conditions, however, led only to recovery of unreacted starting material (54%), indicating that the furan cleavage reaction is strongly influenced by the presence of the C-5 methyl group. When ozone was passed directly into a solution of **3a-b** in methanol at -78 °C, and the solution was subsequently treated with dimethyl sulfide, the pyruvoyl compounds (**20a,b**) were formed in 30-32% yields. Under the same conditions, **21a,b-22a,b** were likewise produced from **4a,b-5a,b** in yields summarized in Table 1.

Table 1 Ozonolysis of furans (**3-6**) in methanol to diketones (**20-22**)



20a R^2 = Ac, X = H
20b R^2 = CO_2Bn, X = H
21a R^2 = Ac, X = OMe
21b R^2 = CO_2Bn, X = OMe
22a R^2 = Ac, X =Cl
22b R^2 = CO_2Bn, X = Cl

Substrate	Product	Yield (%)
3a	**20a**	31
3b	**20b**	30
4a	**21a**	29
4b	**21b**	28
5a	**22a**	19
5b	**22b**	19
6a	**20a**	15
6b	**20b**	15

The method described herein affords modest yields of pyruvoyl derivatives from 2,4,5-trimethylfuryl and 2,4-dimethylfuryl substituents in yields higher than that previously described (14%) for the oxidation of 2,5-diphenylfuran to phenylglyoxal.[7] Nevertheless, we consider that application of this methodology to achieve our ultimate synthetic objective (preparation of the biogenetic precursor 6-pyruvoyl-5,6,7,8- tetrahydropterin (**1**)) will require a more effective furan oxidative procedure. Efforts in this direction are continuing.

EXPERIMENTAL

All melting points were determined using a Büchi 535 apparatus and are uncorrected. Boiling points are uncorrected. Except for compounds (**7**) and (**8**), boiling points refer to oven temperatures for Kugelrohr-distillation. IR spectra were recorded on a JASCO IR-810 spectrophotometer, and NMR spectra were obtained with a JEOL JNM EX270 instrument, using solutions in deuteriochloroform containing tetramethylsilane as the internal standard.

Preparation of acetylfurans

3-Acetyl-2,4,5-trimethylfuran (**7**)

A mixture of 3-hydroxy-2-butanone dimer (acetoin) (19.6 g, 0.22 mol), 2,4-pentanedione (25.0 g, 0.25 mol) and zinc chloride (20 g, 0.15 mol) in ethanol (32 mL) was stirred under reflux for 1 h. After cooling to rt, the solution was poured into ice-water, and the resulting solution was extracted with benzene (3 × 50 mL). The extract was washed with water and dried over $MgSO_4$. After evaporation of benzene *in vacuo*, the residue was distilled to give a colorless oil (30.2 g, 89%). Compound (**7**): bp 98-100 °C (10 Torr); ^{1}H-NMR: δ 2.08 (3H, s), 2.16 (3H, s), 2.41 (3H, s), 2.51 (3H, s). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.76; H, 7.64.

3-Acetyl-2,4-dimethylfuran (**8**)

A mixture of 95% 1-hydroxy-2-propanone (hydroxyacetone) (17.0 g, 0.22 mol), 2,4-pentanedione (24.0 g, 0.24 mol) and zinc chloride (17 g, 0.12 mol) in ethanol (30 mL) was treated as described above to give a colorless oil (27.9 g, 93%). Compound (**8**): bp 85-86 °C (16 Torr); ^{1}H-NMR: δ 2.17 (3H, s), 2.43 (3H, s), 2.55 (3H, s), 7.03 (1H, s). Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.47; H, 7.37.

Preparation of Schiff bases

N-[1-(2',4',5'-Trimethylfur-3'-yl)ethylidene]aniline (**9**)

A mixture of **7** (4.02 g, 26 mmol), distilled aniline (2.6 g, 28 mmol), *p*-toluenesulfonic acid monohydrate (20 mg, 0.1 mmol) and powdered 4Å molecular sieves (7 g) in benzene (30 mL) was stirred and heated under reflux for 20 h. After being cooled to rt, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was subjected to flash chromatography on silica gel (45 g), eluting with 9:1 hexane/ethyl acetate, to afford the imine (**9**) (3.85 g, 64%). Distillation gave a pale yellow oil. Compound (**9**): bp 90 °C (10 Torr); IR (neat): ν_{max} 1650 cm^{-1} (C=N); ^{1}H-NMR: δ 2.07 (6H, s), 2.18 (3H, s), 2.44 (3H, s), 6.74-6.78 (2H, m), 7.05-7.07 (1H, m), 7.29-7.35 (2H, m); ^{13}C-NMR: δ 10.3, 11.1, 14.0, 20.5, 113.7, 119.4, 120.7, 122.9, 128.3, 128.9, 145.6, 151.5, 163.1. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.31; H, 7.59; N, 6.19.

The following compounds were prepared by the above procedure.

4-Methoxy-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethylidene]aniline (**10**)

This compound was obtained from 4-methoxyaniline and **7** in 61% yield as colorless needles after recrystallization from hexane. Compound (**10**): mp 85-86 °C; IR (KBr): ν_{max}1620 cm^{-1} (C=N); ^{1}H-NMR: δ 2.06 (3H, s), 2.08 (3H, s), 2.18 (3H, s), 2.44 (3H, s), 3.80 (3H, s), 6.68-6.73 (2H, m), 6.87-6.90 (2H, m);

^{13}C-NMR: δ 10.3, 11.1, 13.9, 20.5, 55.5, 113.6, 114.2, 120.7, 122.1, 123.5, 144.7, 145.5, 155.7, 163.5. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.65; H, 7.48; N, 5.38.

4-Chloro-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethylidene]aniline (**11**)

This compound was obtained from 4-chloroaniline and **7** in 52% yield as pale yellow needles from recrystallization from hexane. Compound (**11**): mp 84 °C; IR (KBr): ν_{max} 1620 cm^{-1} (C=N); ^{1}H-NMR: δ 2.06 (3H, s), 2.07 (3H, s), 2.18 (3H, s), 2.44 (3H, s), 6.61-6.71 (2H, m), 7.26-7.30 (2H, m); ^{13}C-NMR: δ 10.3, 11.0, 14.1, 20.6, 113.6, 120.8, 122.1, 128.1, 128.5, 129.0, 145.8, 150.0, 163.8. Anal. Calcd for $C_{15}H_{16}NOCl$: C, 68.83; H, 6.16; N, 5.35. Found: C, 68.91; H, 6.21; N, 5.37.

N-[1-(2',4'-Dimethylfur-3'-yl)ethylidene]aniline (**12**)

This compound was obtained from aniline and **8** in 66% yield as colorless needles after recrystallization from hexane. Compound (**12**): mp 35-35.5 °C; IR (KBr): ν_{max} 1630 cm^{-1} (C=N); ^{1}H-NMR: δ 2.09 (3H, s), 2.15 (3H, s), 2.49 (3H, s), 6.76-6.79 (2H, m), 7.03-7.08 (2H, m), 7.31-7.36 (2H, m); ^{13}C-NMR: δ 10.5, 14.3, 20.6, 119.4, 120.1, 123.0, 128.4, 128.9, 137.6, 137.7, 151.3, 153.0, 162.9. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.78; H, 7.13; N, 6.53.

Preparation of furylethylanilines

N-[1-(2',4',5'-Trimethylfur-3'-yl)ethyl]aniline (**13**)

Sodium borohydride (0.756 g, 20 mmol) was added to a solution of imine (**9**) (2.13 g, 9.4 mmol) in distilled methanol (50 mL) under argon, and the mixture was stirred at rt for 2 h. After evaporation *in vacuo*, ethyl acetate (100 mL) was added to the residue, and the solution was washed with several portions of water. Drying over $MgSO_4$ followed by evaporation *in vacuo* gave an oil, which was distilled to yield a pale yellow oil (1.78 g, 83%). Compound (**13**): bp 70 °C (8 Torr); IR (neat): ν_{max} 3420 cm^{-1} (N-H); ^{1}H-NMR: δ 1.45 (3H, d, J = 6.6 Hz), 1.92 (3H, s), 2.10 (3H, s), 2.23 (3H, s), 3.75 (1H, br s), 4.35 (1H, q, J = 6.6 Hz), 6.50-6.53 (2H, m), 6.62-6.67 (1H, m), 7.08-7.13 (2H, m); ^{13}C-NMR: δ 9.0, 11.1, 12.1, 22.3, 45.8, 113.0, 113.2, 117.1, 121.6, 129.1, 144.2,144.9, 147.5. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.53; N, 6.11. Found: C, 78.63; H, 8.40; N, 6.06.

The following compounds were prepared by the above procedure.

4-Methoxy-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**14**)

This compound was obtained from **10** in 77% yield as a pale yellow oil after distillation. Compund (**14**): bp 160 °C (5 Torr); IR (neat): ν_{max} 3430 cm^{-1} (N-H); ^{1}H-NMR: δ 1.45 (3H, d, J = 6.6 Hz), 1.93 (3H, s), 2.11 (3H, s), 2.23 (3H, s), 3.72 (3H, s), 4.30 (1H, q, J = 6.6 Hz), 6.48-6.51 (2H, m), 6.70-6.74 (2H, m); ^{13}C-NMR: δ 9.1, 11.2, 12.1, 22.5, 46.6, 55.7, 113.2, 114.4, 114.7, 121.7, 141.9, 144.3, 144.9, 151.9. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.72; H, 8.22; N, 5.35.

4-Chloro-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**15**)

This compound was obtained from **11** in 93% yield as a colorless oil after distillation. Compound (**15**): bp 160

°C (3 Torr); IR (neat): ν_{max} 3420 cm^{-1} (N-H); ^{1}H-NMR: δ 1.46 (3H, d, *J* = 6.9 Hz), 1.91 (3H, s), 2.11 (3H, s), 2.22 (3H, s), 3.78 (1H, br s), 4.31 (1H, q, *J* = 6.9 Hz), 6.41-6.45 (2H, m), 7.03-7.06 (2H, m); ^{13}C-NMR: δ 9.0, 11.1, 12.1, 22.4, 46.0, 113.0, 114.1, 121.1, 121.7, 128.9, 144.3, 145.1, 146.0. Anal. Calcd for $C_{15}H_{18}NOCl$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.22; H, 6.87; N, 5.19.

N-[1-(2',4'-Dimethylfur-3'-yl)ethyl]aniline (**16**)

This compound was obtained from **12** in 93% yield as a pale yellow oil after distillation. Compound (**16**): bp 75 °C (5 Torr); IR (neat): ν_{max} 3420 cm^{-1} (N-H); ^{1}H-NMR: δ 1.48 (3H, d, *J* = 6.6 Hz), 2.01 (3H, s), 2.26 (3H, s), 3.77 (1H, br s), 4.40 (1H, q, *J* = 6.6 Hz), 6.50-6.53 (2H, m), 6.63-6.68 (1H, m), 6.98 (1H, s), 7.08-7.14 (2H, m); ^{13}C-NMR: δ 9.1, 12.3, 22.4, 45.6, 112.9, 117.2, 119.4, 121.3, 129.1, 137.2, 147.4, 147.5. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.16; H, 7.97; N, 6.50.

Acetylation of furylethylanilines

N-Acetyl-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**3a**)

A mixture of **13** (2.00 g, 8.7 mmol) and 4-dimethylaminopyridine (30 mg) in distilled acetic anhydride (20 mL, 0.21 mol) and dry pyridine (10 mL, 0.12 mol) was stirred and heated at 60 °C for 2 h. After cooling to rt, methanol (30 mL) was added, and the mixture was evaporated *in vacuo*. To the residue was added ethyl acetate (100 mL), and the solution was washed with aqueous 2% copper sulfate, saturated aqueous sodium hydrogen carbonate and then several portions of water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel (45 g), eluted with 3:1 hexane/ethyl acetate, and the eluate evaporated to give **3a** (2.06 g, 87%). The analytical sample was obtained by recrystallization from hexane as colorless scaly crystals. Compound (**3a**): mp 48 °C; IR (KBr): ν_{max} 1650 cm^{-1} (C=O); ^{1}H-NMR: δ 1.46 (3H, d, *J* = 7.3 Hz), 1.68 (3H, s), 1.71 (3H, s), 1.75 (3H, s), 2.11 (3H, s), 6.10 (1H, q, *J* = 7.3 Hz), 7.27-7.38 (5H, m); ^{13}C-NMR: δ 8.6, 11.2, 12.5, 17.7, 23.1, 45.6, 115.0, 118.7, 128.1, 128.8, 130.5, 139.1, 144.2, 147.5, 169.3. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.25; H, 7.92; N, 5.09.

The following compounds were prepared by the above procedure.

N-Acetyl-4-methoxy-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**4a**)

This compound was obtained from **14** in 86% yield as colorless prisms after recrystallization from hexane. Compound (**4a**): mp 94-95 °C; IR (KBr): ν_{max} 1650 cm^{-1} (C=O); ^{1}H-NMR: δ 1.43 (3H, d, *J* = 7.3 Hz), 1.69 (3H, s), 1.75 (3H, s), 2.11 (3H, s), 3.81 (3H, s), 6.07 (1H, q, *J* = 7.3 Hz), 6.75 (2H, br s), 7.04 (2H, br s); ^{13}C-NMR: δ 8.7, 11.2, 12.7, 17.6, 23.1, 45.4, 55.4, 115.0, 118.8, 131.4, 131.7, 144.1, 147.5, 159.2, 169.8. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.79; H, 7.78; N, 4.59.

N-Acetyl-4-chloro-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**5a**)

This compound was obtained from **15** in 88% yield as colorless prisms after recrystallization from hexane. Compound (**5a**): mp 123-124 °C; IR (KBr): ν_{max} 1640 cm^{-1} (C=O); ^{1}H-NMR: δ 1.45 (3H, d, *J* = 7.3 Hz), 1.69 (3H, s), 1.75 (3H, s), 1.76 (3H, s), 2.11 (3H, s), 6.07 (1H, q, *J* = 7.3 Hz), 7.30 (4H, br s); ^{13}C-NMR: δ 8.6, 11.2, 12.7, 23.1, 45.8, 114.8, 118.4, 129.1, 131.8, 134.2, 137.6, 144.5, 147.5, 169.1. Anal. Calcd for

$C_{17}H_{20}NO_2Cl$: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.78; H, 6.76; N, 4.40.

N-Acetyl-*N*-[1-(2',4'-dimethylfur-3'-yl)ethyl]aniline (**6a**)

This compound was obtained from **16** in 69% yield as a colorless oil after distillation. Compound (**6a**): bp 80 °C (5 Torr); IR (neat): ν_{max} 1660 cm^{-1} (C=O); ^{1}H-NMR: δ 1.48 (3H, d, *J* = 7.3 Hz), 1.69 (3H, s), 1.76 (3H, s), 1.81 (3H, s), 6.16 (1H, q, *J* = 7.3 Hz), 6.94 (1H, s), 7.29-7.44 (5H, m); ^{13}C-NMR: δ 8.7, 12.7, 17.6, 23.1, 45.2, 45.3, 118.4, 121.3, 128.2, 128.9, 130.5, 136.5, 139.0, 150.7, 169.3. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.40; H, 7.46; N, 5.44.

Benzyloxycarbonylation of furylethylanilines

N-Benzyloxycarbonyl-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**3b**)

Benzyl chloroformate (0.28 mL, 2.0 mmol) was added to a solution of **13** (0.200 g, 0.87 mmol) in dry pyridine (1.5 mL) at 0 °C under argon, and the mixture was stirred at 0 °C for 30 min. After further stirring at rt for 1 h, the mixture was diluted with ice water (20 mL), and extracted with chloroform (3 × 10 mL). The extracts were washed with aqueous 2% copper sulfate, saturated sodium hydrogen carbonate solution and then several portions of water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography over Florisil (5 g) (elution with 3:1 hexane/ethyl acetate), and then by HPLC (10 μ silica gel, 2.2 × 30 cm) (elution with 9:1 hexane/ethyl acetate), to afford **3b** (0.276 g, 87%), which was distilled to provide a yellow oil. Compound (**3b**): bp 130 °C (7 Torr); IR (neat): ν_{max} 1700 cm^{-1} (C=O); ^{1}H-NMR: δ 1.49 (3H, d, *J* = 7.3 Hz), 1.67 (3H, s), 1.71 (3H, s), 2.10 (3H, s), 5.12 (2H, s), 5.67 (1H, q, *J* = 7.3 Hz), 6.80-6.84 (2H, m), 7.17-7.27 (8H, m); ^{13}C-NMR: δ 8.6, 11.2, 12.6, 18.2, 48.8, 66.8, 114.8, 118.8, 127.1, 127.4, 127.5, 128.2, 128.3, 130.4, 137.0, 137.7, 144.2, 147.2, 155.1. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 75.93: H, 6.94; N, 3.92.

The following compounds were prepared by the above procedure.

N-Benzyloxycarbonyl-4-methoxy-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**4b**)

This compound was obtained from **14** in 82% yield as colorless crystals after recrystallization from hexane. Compound (**4b**): mp 67 °C; IR (KBr): ν_{max} 1685 cm^{-1} (C=O); ^{1}H-NMR: δ 1.47 (3H, d, *J* = 7.3 Hz), 1.68 (3H, s), 1.75 (3H, s), 2.11 (3H, s), 3.79 (3H, s) 5.11 (2H, s), 5.64 (1H, q, *J* = 7.3 Hz), 6.70-6.80 (4H, m), 7.19-7.26 (5H, m); ^{13}C-NMR: δ 8.6, 11.2, 18.2, 48.7, 55.3, 66.8, 113.5, 114.8, 118.9, 127.2, 127.5, 128.2, 130.4, 131.3, 137.1, 144.2, 147.2, 155.4, 158.7. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.18; 6.96; N, 3.57.

N-Benzyloxycarbonyl-4-chloro-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**5b**)

This compound was obtained from **15** in 44% yield as colorless oil after distillation. Compound (**5b**): bp 210 °C (4 Torr); IR (neat): ν_{max} 1705 cm^{-1} (C=O); ^{1}H-NMR: δ 1.48 (3H, d, *J* = 7.3 Hz), 1.68 (3H, s), 1.77 (3H, s), 2.11 (3H, s), 5.11 (2H, s), 5.65 (1H, q, *J* = 7.3 Hz), 6.73-6.76 (2H, m), 7.19-7.30 (7H, m); ^{13}C-NMR: 8.6, 11.2, 12.8, 18.2, 48.9, 67.1, 114.7, 118.6, 127.3, 127.8, 128.3, 128.6, 131.7, 133.4, 136.4, 136.7, 144.5, 147.2, 154.9. Anal. Calcd for $C_{23}H_{24}NO_3Cl$: C, 69.43; H, 6.08; N, 3.52. Found: C, 69.21; H, 6.08; N, 3.40.

N-Benzyloxycarbonyl-*N*-[1-(2',4'-dimethylfur-3'-yl)ethyl]aniline (**6b**)

This compound was obtained from **16** in 62% yield as a pale yellow oil after distillation. Compound (**6b**): bp 120 °C (5 Torr); IR (neat): ν_{max} 1700 cm^{-1} (C=O); ^{1}H-NMR: δ 1.52 (3H, d, *J* = 7.3 Hz), 1.69 (3H, s), 1.81 (3H, s), 5.12 (2H, s), 5.73 (1H, q, *J* = 7.3 Hz), 6.81-6.83 (2H, m), 6.93 (1H, s), 7.17-7.28 (8H, m); ^{13}C-NMR: δ 8.7, 12.8, 18.2, 48.4, 66.5, 118.5, 121.2, 127.1, 127.5, 128.3, 128.4, 130.4, 136.5, 136.6, 136.9, 137.6, 150.5, 155.1. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63: N, 4.01. Found: C, 75.68; H, 6.57; N, 4.03.

Reaction of *N*-acetyl-*N*-[1-(2',4',5'-trimethylfur-3'-yl)ethyl]aniline (**3a**) with *m*-CPBA.

m-CPBA (89%, 0.448 g, 2.0 mmol) was added to a solution of **3a** (0.271 g, 1.0 mmol) in dichloromethane (6 mL) below 0 °C, and the mixture was stirred at that temperature for 1 h and then diluted with aqueous sodium thiosulfate (1.0 mol/L, 12 mL). The mixture was extracted with chloroform (3 × 10 mL), and the extracts were washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by chromatography over Florisil (10 g) (elution with 1:1 hexane/ethyl acetate) and then by HPLC (10 μ silica gel, 2.2 × 30 cm) (elution with 2:1 hexane/ethyl acetate), to afford **18** or its isomer **19** (0.152 g, 50%), which was distilled to furnish a colorless oil. Compound (**18** or **19**): bp 110 °C (4 Torr); ^{1}H-NMR: δ 1.12 (3H, d, *J* = 7.3 Hz), 1.81 (3H, s), 1.86 (3H, s), 2.03 (3H, s), 2.17 (3H, s), 5.52 (1H, q, *J* = 7.3 Hz), 7.30-7.43 (5H, m); ^{13}C-NMR: δ 14.5, 14.8, 17.7, 21.0, 22.9, 59.2, 122.8, 128.2, 129.1, 129.9, 140.2, 148.1, 168.9, 170.6, 201.5. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.39; H, 7.07; N, 4.66.

Ozonolysis in dichloromethane

N-Benzyloxycarbonyl-*N*-[1-(1-pyruvoyl)ethyl]aniline (**20b**)

Ozone-oxygen gas was passed into dichloromethane (25 mL) at -78 °C until the solution became deep blue, at which point the concentration of ozone was shown to be 4.22 mole/L.[8] To the solution was added a mixture of **6b** (0.175 g, 0.5 mmol) and dichloromethane (5 mL) at -78 °C, and the solution was stirred for 30 min. Dimethyl sulfide (0.08 mL, 1.1 mmol) was added, and the resulting mixture was stirred for 1 h. The temperature was gradually raised to rt over a period of 2 h. After stirring for 1 h, the mixture was evaporated *in vacuo*. The residue was purified by chromatography over Florisil (5 g) (elution with 3:1 hexane/ethyl acetate) and then by HPLC (10 μ silica gel, 2.2 × 30 cm) (elution with 9:1 hexane/ethyl acetate), to afford **20b** (0.026 g, 16%), which was recrystallized from hexane as colorless needles. Compound (**20b**): mp 67 °C; IR (KBr): ν_{max} 1730, 1720 cm^{-1} (C=O); ^{1}H-NMR: δ 1.42 (3H, d, *J* = 6.6 Hz), 2.25 (3H, s), 4.54 (1H, s), 5.05 (2H, dd, *J* = 19.1, 12.5 Hz), 7.16-7.44 (10H, m); ^{13}C-NMR: δ 13.6, 23.8, 60.7, 67.7, 127.2, 127.7, 127.9, 128.4, 129.2, 136.1, 140.5, 155.4, 196.0, 198.6. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: 70.22; H, 5.91; N, 4.27.

Further elution gave the starting material (9 mg, 5%).

Ozonolysis in methanol

N-Acetyl-*N*-[1-(1-pyruvoyl)ethyl]aniline (**20a**)

Ozone-oxygen (ozone: 0.03 mmol/min) was passed into a solution of **3a** (0.135 g, 0.5 mmol) in distilled

methanol (50 mL) at -78 °C for 30 min (ozone: 1.0 mmol), and dimethyl sulfide (0.08 mL, 1.143 mmol) was added. The mixture was worked up in the above manner affording diketone (**20a**) (0.036 g, 31%), which was recrystallized from hexane as pale yellow microcrystals. Compound (**20a**): mp 48 °C; IR (KBr): ν_{max} 1700 cm^{-1} (C=O); ^{1}H-NMR: δ 1.39 (3H, d, *J* = 6.6 Hz), 1.77 (3H, s), 2.44 (3H, s), 4.35 (1H, q, *J* = 6.6 Hz), 7.44-7.48 (5H, m); ^{13}C-NMR: δ 13.6, 23.8, 60.7, 67.7, 127.2, 127.9, 128.3, 129.2, 136.1, 140.5, 155.4, 196.0, 198.6. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.77; H, 6.56; N, 5.84.

The following compounds were prepared by the above procedure.

N-Acetyl-4-methoxy-*N*-[1-(1-pyruvoyl)ethyl]aniline (**21a**)
This compound was obtained from **4a** in 29% yield as pale yellow crystals after recrystallization from hexane. Compound (**21a**): mp 62-63 °C; IR (KBr): ν_{max} 1710 cm^{-1} (C=O) ^{1}H-NMR: δ 1.37 (3H, d, *J* = 6.6 Hz), 1.76 (3H, s), 2.43 (3H, s), 3.85 (3H, s), 4.31 (1H, q, *J* = 6.6 Hz), 6.95-6.98 (2H, m), 7.28-7.36 (2H, m); ^{13}C-NMR: δ 13.3, 21.7, 23.6, 55.5, 59.6, 114.9, 129.4, 134.2, 159.5, 171.2, 194.0, 198.0. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.76; H, 6.57; N, 5.28.

N-Benzyloxycarbonyl-4-methoxy-*N*-[1-(1-pyruvoyl)ethyl]aniline (**21b**)
This compound was obtained from **4b** in 28% yield as a yellow oil after distillation. Compound (**21b**): bp 170 °C (3 Torr); IR (neat): ν_{max} 1720, 1710 cm^{-1} (C=O); ^{1}H-NMR: δ 1.39 (3H, d, *J* = 6.6 Hz), 2.25 (3H, s), 3.81 (3H, s), 4.46 (1H, q, *J* = 6.6 Hz), 5.03 (2H, dd, *J* = 12.5, 20.5 Hz), 6.89-6.92 (2H, m), 7.13-7.15 (2H, m), 7.27-7.31 (5H, m); ^{13}C-NMR: δ 13.5, 23.8, 55.4, 60.8, 67.6, 114.3, 127.1, 127.9, 128.3, 129.0, 133.2, 136.2, 158.8, 196.0, 198.6. Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96: N, 3.94. Found: C, 67.58; H, 6.02; N, 3.90.

N-Acetyl-4-chloro-*N*-[1-(1-pyruvoyl)ethyl]aniline (**22a**)
This compound was obtained from **5a** in 19% yield as pale yellow prisms after recrystallization from hexane. Compound (**22a**): mp 78-79 °C; IR (KBr): ν_{max} 1710 cm^{-1} (C=O); ^{1}H-NMR: δ 1.37 (3H, d, *J* = 6.6 Hz), 1.77 (3H, s), 2.43 (3H, s), 4.31 (1H, q, *J* = 6.6 Hz), 7.37-7.48 (4H, m); ^{13}C-NMR: δ 13.4, 21.8, 23.7, 59.7, 129.7, 130.2, 134.8, 140.0, 170.6, 193.7, 198.0. Anal. Calcd for $C_{13}H_{14}NO_3Cl$: C, 58.33: H, 5.27; N, 5.23. Found: C, 58.27; H, 5.25; N, 5.15.

N-Benzyloxycarbonyl-4-chloro-*N*-[1-(1-pyruvoyl)ethyl]aniline (**22b**)
This compound was obtained from **5b** in 19% yield as colorless needles after recrystallization from hexane. Compound (**22b**): mp 78.5-79 °C; IR (KBr): ν_{max} 1720, 1710 cm^{-1} (C=O); ^{1}H-NMR: δ 1.40 (3H, d, *J* = 6.6 Hz), 2.26 (3H, s), 4.49 (1H, br s), 5.05 (2H, dd, *J* = 12.5, 19.1 Hz), 7.16 (2H, br s), 7.30-7.39 (7H, m); ^{13}C-NMR: δ 13.6, 23.8, 60.7, 67.9, 127.3, 128.1, 128.5, 129.3, 133.5, 135.8, 139.0, 155.2, 195.7, 198.5. Anal. Calcd for $C_{19}H_{18}NO_4Cl$: C, 63.42; H, 5.04; N, 3.89. Found: C, 63.18; H, 5.03; N, 3.81.

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