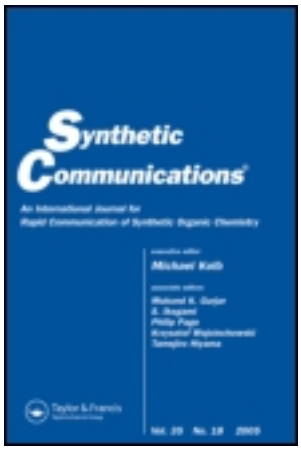

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A CONVENIENT METHOD FOR THE PREPARATION OF α-KETOACETALS

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ABSTRACT

A convenient method for the preparation of α-ketoacetal derivatives **2a–g** was developed by addition of Grignard reagent (**1a–g**) to commercially available ethyl diethoxyacetate (**3**) in 60–96% yield.

Key Words: α-Ketoacetals; Imidazo[1,2-*a*]pyrazin-3(*7H*)-one; Grignard reaction; Ethyl diethoxyacetate

INTRODUCTION

α-Ketoacetals (protected glyoxal derivatives, **2**) are important synthons for constructing nitrogen containing heterocycles including 3,5-dihydro-imidazol-4-one,[1] 4,5-dihydro-1(3H)-imidazole-4,5-diol,[1] 2H-imidazo[1,2-*a*]pyridin-3-one,[2] imidazo[1,2-*a*]pyrimidine,[3] imidazo[1,2-*b*]pyridazine,[3–5]

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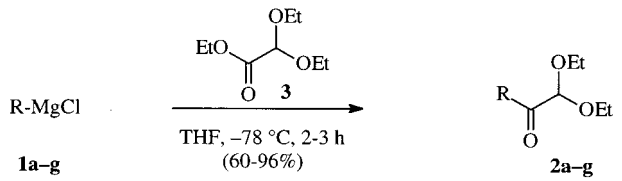
4,5-dihydroxy-imidazolidin-2-one,[6] and imidazo[1,2-*a*]pyrazin-3(7*H*)-one.[7,8] The imidazo[1,2-*a*]pyrazin-3(7*H*)-one system is particularly interesting since it is the nucleus of the coelenterazine-type chemiluminophores that are necessary for the function of photoproteins and luciferins found in a variety of light producing organisms.[9–11] We needed a flexible method for preparation of α-ketoacetal derivatives (**2**) for our program on the synthesis of these novel chemiluminophores.

The classical approach to the preparation of α-ketoacetals is based on the work of Wohl and Lang.[12] The reaction of 1-(diethoxyacetyl)piperidine with Grignard reagents proceeds with displacement of the piperidine to afford the α-ketoacetal in moderate yield.[7,13–16] Dulou[17] took a similar approach, reacting Grignard reagents with diethoxyacetonitrile. In these reports both α-ketoacetal precursors were prepared from readily available ethyl diethoxyacetate. In fact, dialkoxyacetates react with metal salts of activated methylene substrates to give the α-ketoacetals directly.[18–28] Within this context, we describe a general, convenient and direct method for preparation of α-ketoacetal derivatives **2a–g** by addition of Grignard reagents (**1a–g**) to a commercially available, inexpensive, ethyl diethoxyacetate (**3**).



Scheme 1.

Typically, the THF solution of magnesium chloride reagent (**1**, 1.5 equiv.) (Sch. 1) was added slowly to ethyl diethoxyacetate (**3**) in THF at −78°C temperature under nitrogen with vigorous stirring. After 1–2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution at −78°C and the crude product was purified by silica gel column chromatography. The method afforded excellent yields of α-ketoacetal derivatives (**2a–g**) (Table 1) with a variety of substrates in 60–96% yield. The reaction was also carried out with 1 : 1 ratio of Grignard reagent (**1**) and ethyl diethoxyacetate (**3**), however, the yields of α-ketoacetal derivatives (e.g., **2e**) were 10–15% lower, and under these conditions the unreacted starting material **3** was also recovered in 10% yield. The substrates containing a variety of R groups such as *n*-alkyl (Entries 1–2), olefinic (Entry 3) secondary alkyl (Entries 4), benzylic (Entries 5) and halosubstituted benzylic

Table 1. Preparation of α-Ketoacetal Derivatives **2a–g**

S.No.	Grignard Reagent (**1**) R =	Reaction Conditions Sol/Time (h)/Temp. (°C)	α-Ketoacetals (**2**) Yield (%)[a]	
1	**1a** CH_3CH_2	THF/2/−78	**2a**	66
2	**1b** $CH_3(CH_2)_2CH_2$	THF/2/−78	**2b**	65
3	**1c** $CH_2{=}CHCH_2$	THF/2/−78	**2c**	76
4	**1d** $CH_3CH_2(CH_3)CH$	THF/2/−78	**2d**	64
5	**1e** $C_6H_5CH_2$	THF/2/−78	**2e**	96
6	**1f** *p*-F-$C_6H_4CH_2$[b]	THF/2/−78	**2f**	85
7	**1g** *p*-MeO-$C_6H_4CH_2$	THF/3/−78	**2g**	60

[a]Isolated yield; [b]Grignard reagent was prepared from *p*-F-$C_6H_4CH_2Cl$ and Mg in THF.

(Entries 6,7) were prepared in good yield, which show the generality of the method. The reaction of isopropenylmagnesium bromide, phenyl magnesium and *p*-tolylmagnesium bromide reagents with ethyl diethoxyacetate (**3**) gave the corresponding the tertiary alcohols. Therefore, use of less nucleophilic magnesium chloride reagents was necessary. Finally, the reaction work-up procedure is simple and involved short silica gel column chromatography purification.

In summary, a convenient method for the preparation of α-ketoacetal derivatives **2a–g** was developed from the reaction of commercially available ethyl diethoxyacetate and Grignard reagents in 60–96% yield.

EXPERIMENTAL

General methods and materials: ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz) and the chemical shifts (δ) reported in ppm relative to TMS. Electrospray ionization mass spectrometry (ESI-MS) was carried out on a Perkin-Elmer (Norwalk, CT) Sciex API 100 Benchtop system employing Turbo IonSpray ion source and HRMS were obtained on a Nermang 3010 MS-50, JEOL SX102-A. Thin layer chromatography was performed on a pre-coated Whatman MK6F silica gel 60 Å plates (layer thickness: 250 μm) and visualized with UV light and/or using $KMnO_4$ solution [prepared by dissolving $KMnO_4$ (2.0 g) and $NaHCO_3$ (8.0 g) in water (200 mL)]. Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). THF was freshly distilled from a purple solution of sodium and benzophenone under nitrogen. All reagents were purchased from Aldrich Chemical Co.

(Milwaukee, WI) or Sigma Chemical Co. (St. Louis, MO). 4-Methoxybenzylmagnesium chloride (0.25 M in THF solution was purchased from Rieke Metals Inc., Lincoln, NE. All the solvents employed were of HPLC grade purchased from EM Science (Gibbstown, NJ).

General procedure for preparation of α-ketoacetal derivatives (2a–g), e.g., 2e: In a 100 mL oven dried round bottom flask equipped with stir bar and nitrogen inlet, ethyl diethoxyacetate (**3**, 1.76 g, 10.0 mmol) was dissolved in THF (40 mL) and cooled to −78°C (dry ice-acetone bath). To this mixture, benzyl magnesium chloride **1e** (2.0 M soln in THF, 7.5 mL, 15.0 equiv., 1.5 equiv.) was added under nitrogen via syringe slowly over a 10 min period. The resulting pale yellow reaction mixture was stirred for 2 h and quenched with 20% aqueous NH_4Cl solution (10 mL) at −78°C. The mixture was allowed to warm to room temperature and diluted with EtOAc (50 mL) and water (50 mL). Organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed on a rotary evaporator. The crude compound was purified by silica gel column chromatography (10% EtOAc in hexanes) to afford 2.167 g of 1,1-diethoxy-3-phenylacetone (**2e**) in 96% yield as colorless viscous oil.

1,1-Diethoxy-2-butanone (2a):[17,29] Yield: 1.063 g (66%, colorless viscous oil); R_f: 0.60 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$): δ 4.55 (s, 1H, s), 3.67–3.63 (m, 2H), 3.58–3.52 (m, 2H), 2.59 (q, 2H, $J = 7.5$ Hz), 1.21 (6H, t, $J = 7.2$ Hz), 1.02 (3H, t, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$): δ 206.8, 102.5, 63.1, 30.0, 15.0, 6.9; ESI-MS (m/z): 178 $(M + NH4)^+$. Lit.[29] ^{1}H NMR (CCl_4): δ 4.32 (s, 1H), 3.3–3.8 (m, 4H), 2.51 (q, 2H, $J = 7.1$ Hz), 1.17 (t, 6H, $J = 6.8$ Hz), 0.97 (t, 3H, $J = 7.1$ Hz); M.S. (m/e rel. intens. %): no $(M)^+$, 115 (1), 103 (13), 97 (5), 75 (24), 59 (6), 57 (9), 47 (100), 41 (10).

1,1-Diethoxy-2-hexanone (2b):[26,30] Yield: 1.23 g (65%, colorless viscous oil); R_f: 0.57 (10% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$): δ 4.55 (s, 1H), 3.74–3.64 (m, 2H), 3.60–3.50 (m, 2H), 2.58 (t, 2H, $J = 7.2$ Hz), 1.62–1.50 (m, 2H), 1.38–1.22 (m, 2H), 1.24 (t, 6H, $J = 7.2$ Hz), 0.90 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 206.5, 102.7, 63.3, 36.5, 25.1, 22.3, 15.1, 13.8; ESI-MS (m/z): 189 $(M)^+$, 206 $(M + NH_4)^+$. Lit.[30] IR: 1725 cm^{-1} (C=O), 1100 cm^{-1} (C-O); ^{1}H NMR ($CDCl_3$): δ 4.6 (s, 1H), 3.6 (m, 4H), 2.5 (t, 2H), 1–1.5 (m, 10H), 0.9 (t, 3H).

1,1-Diethoxy-4-penten-2-one (2c): Yield: 1.309 g, (76%, colorless viscous oil); R_f: 0.38 (15% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$): δ 6.00–5.87 (m, 1H), 5.22–5.12 (m, 2H), 4.61 (s, 1H), 3.76–3.66 (m, 2H), 3.62–3.52 (m, 2H), 3.40–3.36 (m, 2H), 1.26 (t, 3H, $J = 7.2$ Hz), 1.25 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 203.7, 129.9, 118.7, 102.2, 63.2, 41.5, 15.0; ESI-MS (m/z): 173 $(M + H)^+$, 190 $(M + NH_4)^+$; Anal. Calcd. for $C_9H_{16}O_3$: C, 62.77; H, 9.36; Found: C, 62.48; H, 9.11.

1,1-Diethoxy-3-methyl-2-pentanone (2d):[13,31] Yield: 1.20 g (64%, colorless viscous oil); R_f: 0.69 (20% EtOAc in hexanes); ^{1}H NMR ($CDCl_3$): δ 4.60 (s, 1H), 3.68–3.61 (m, 2H), 3.58–3.50 (m, 2H), 2.87 (q, 1H, $J = 6.8$ Hz), 1.72–1.63 (m, 1H), 1.37–1.29 (m, 1H), 1.21 (t, 6H, $J = 7.0$ Hz), 1.05 (d, 3H, $J = 6.9$ Hz), 0.83 (t, 3H, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 209.3, 102.1, 63.1, 62.9, 42.0, 25.8, 16.1, 15.0, 11.5; ESI-MS (m/z): 206 $(M + NH_4)^+$. Lit.[31] (for corresponding dimethylacetal derivative): IR (NaCl): 2842 (OCH_3), 1730 (C=O) cm^{-1};^{1}H NMR (CCl_4): δ 4.30 (s, 1H), 2.8 (m, 1H), 1.6 (m, 2H), 1.83 (t, 3H, $J = 7$ Hz), 1.02 (d, 3H, $J = 6$H); mass spectrum m/e (rel intensity): no (M)+, 129 (3), 114 (25), 101 (3), 96 (9), 85 (4), 75 (100), 71 (16), 69 (25), 68 (16), 67 (12), 57 (6), 55 (25).

1,1-Diethoxy-3-phenylacetone (2e):[32] Yield: 2.167 g (96%, colorless viscous oil); R_f: 0.33 (15% EtOAc in hexanes); Analytical RP HPLC (Waters, Novapak, C18, 4.0 μm, 3.9 × 150 mm): MeCN : water : 0.1% aqueous trifluoroacetic acid/70 : 20 : 10, 1.0 mL/min at 215 nm, R_t: 2.18 min, 97%; ^{1}H NMR ($CDCl_3$): δ 7.36–7.20 (m, 5H), 4.63 (s, 1H), 3.89 (s, 2H), 3.76–3.66 (m, 2H), 3.60–3.50 (m, 2H), 1.25 (t, 6H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 203.0, 133.6, 129.6, 128.3, 126.7, 102.2, 63.3, 43.6, 15.0; ESI-MS (m/z): 223 $(M + H)^+$, 240 $(M + NH4)^+$; HRMS (FAB, m/z): Calcd. for $C_{13}H_{18}O_3$, 223.1334 $(M + H)^+$, observed, 223.1330. Lit.[32] b.p.: 143–145°C/12 Torr; IR (CH_2Cl_2): 5.74 μ (C=O), 6.05 μ and 9.42 μ (acetal, ketal).

1,1-Diethoxy-3-(4-fluorophenyl)acetone (2f): Yield: 2.032 g (85%, pale yellow viscous oil); R_f: 0.32 (15% EtOAc in hexanes); Analytical RP HPLC (Waters, Novapak, C18, 4.0 μm, 3.9 × 150 mm column): MeCN : water : 0.1% aqueous trifluoroacetic acid/70 : 20 : 10, 1.0 mL/min at 215 nm, R_t: 2.20 min, 96%; ^{1}H NMR ($CDCl_3$): δ 7.20–7.14 (m, 2H), 7.03–6.97 (m, 2H), 4.62 (s, 1H), 3.86 (s, 2H), 3.77–3.66 (m, 2H), 3.60–3.50 (m, 2H), 1.25 (t, 6H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 202.9, 163.4, 160.2, 131.2, 131.1, 115.3, 115.0, 102.4, 63.4, 42.5, 15.0; ESI-MS (m/z): 258 $(M + NH_4)^+$; HRMS (FAB, m/z): Calcd. for $C_{13}H_{17}FO_3$, 241.1240 $(M + H)^+$, observed, 240.1234.

1,1-Diethoxy-3-(4-methoxyphenyl)acetone (2g): Yield: 1.516 g (60%, pale yellow viscous oil); R_f: 0.38 (20% EtOAc in hexanes); Analytical RP HPLC (Waters, Novapak, C18, 4.0 μm, 3.9 × 150 mm column): MeCN : water/45 : 55, 1.0 mL/min at 220 nm, R_t: 3.83 min, 95%; ^{1}H NMR ($CDCl_3$): δ 7.12 (d, 2H, $J = 8.2$ Hz), 6.85 (2H, d, $J = 8.3$ Hz), 4.61 (s, 1H), 3.8 (s, 2H), 3.77 (s, 3H), 3.70–3.65 (m, 2H), 3.55–3.50 (m, 2H), 1.23 (t, 6H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 203.4, 158.4, 130.6, 125.6, 113.8, 102.1, 63.2, 55.1, 42.7, 15.0; ESI-MS (m/z): 270 $(M + NH_4)^+$; HRMS (EI, m/z): Calcd. for $C_{14}H_{20}O_4$, 252.1362 $(M)^+$, observed, 252.1367.

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