A Convenient Synthesis of Aminomethyl Ketones (α-Amino Ketones)

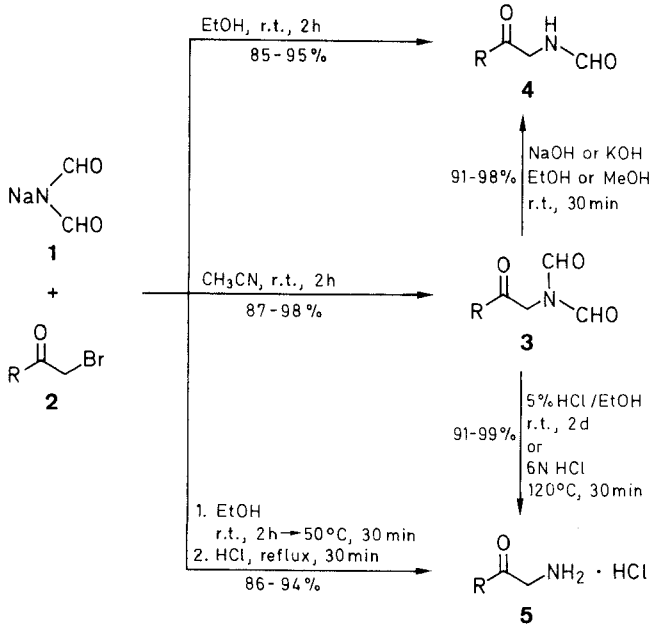
Han Yinglin,* Hu Hongwen

Department of Chemistry, Nanjing University, Nanjing 210008, People's Republic of China

Several *N,N*-diformylaminomethyl ketones **3** were prepared by treating the respective bromomethyl ketone **1** with sodium diformylamide in acetonitrile at room temperature. This reaction produced *N*-formylaminomethyl ketones **4** when ethanol was used as the solvent. One of the formyl groups of *N,N*-diformylaminomethyl ketones was selectively removed by using a catalytic amount of sodium or potassium hydroxide in alcohol to the corresponding *N*-formylaminomethyl ketones **4**. The formyl groups of both *N,N*-diformyl- und *N*-formylaminomethyl ketones could be easily removed by either 5% hydrochloric acid in ethanol or 6N hydrochloric acid to give the corresponding aminomethyl ketone hydrochlorides **5**. These reactions are general and give high yield of the products.

α-Amino ketones are important reagents because they possess both nucleophilic and electrophilic centers, which are useful in the construction of nitrogen-containing heterocycles.[1-4] Numerous methods of preparing these compounds are known and new routes for their synthesis continue to be devised.[5-14] Recently a four-step synthesis of α-amino ketones from α-bromo ketones was reported.[12] Our earlier report[15] on a convenient method for the preparation of primary amines using sodium diformylamide (**1**) as a modified Gabriel reagent has been now extended successfully to the preparation of α-amino ketones.

Thus, *N,N*-diformylaminomethyl ketones **3** were obtained in high yield by treating bromomethyl ketones with **1** in acetonitrile at room temperature. However, *N*-formylaminomethyl ketones **4** were obtained when ethanol was used as the solvent. One of the formyl groups in *N,N*-diformylaminomethyl ketones could be selectively removed by a catalytic amount of sodium or potassium hydroxide in ethanol or methanol at room temperature to give the corresponding *N*-formylaminomethyl ketones in excellent yields. The formyl group of both *N,N*-diformyl- and *N*-formylaminomethyl ketones could be easily removed by 5% hydrochloric acid in ethanol or 6N hydrochloric acid to afford the corresponding aminomethyl ketone hydrochlorides **5**. The latter could also be prepared in one-pot by treating bromomethyl ketones with sodium diformylamide (**1**) in ethanol followed by hydrochloric acid.



2–5	R	2–5	R
a	CH_3	f	$MeOC_6H_4$
b	Ph	g	$2,4\text{-}(CH_3)_2C_6H_3$
c	$4\text{-}BrC_6H_4$	h	$3,4\text{-}(CH_3)_2C_6H_3$
d	$4\text{-}ClC_6H_4$	i	$4\text{-}PhC_6H_4$
e	$4\text{-}CH_3C_6H_4$	j	1-naphthyl

The *N,N*-diformyl- and *N*-formylaminomethyl ketones and aminomethyl ketone hydrochlorides obtained are identified by IR and ^{1}H-NMR spectra (Table). The substituents on the benzene rings have little effect on the yield. In most cases the crude products were obtained in high purity and could be used directly for various purposes. α-Bromopropiophenone does not react with **1** at room temperature, but α-aminopropiophenone and other α-amino ketones could be prepared by the α-alkylation of *N*-formylaminomethyl ketones obtained by the above method. *N,N*-Diformylamino ketones are found to be stable in benzene or absolute ethanol saturated with hydrogen chloride and are not converted into the corresponding aminomethyl ketone hydrochlorides **5**.

In summary, the present method offers a very convenient way to aminomethyl ketones **5**. The reaction is exothermic with efficient cooling it could, however, be carried out on one mole or greater scale. The advantages of this method are mild reaction conditions, easy workup and high yields.

Melting points were measured using a Yanco melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-408 spectrophotometer and ^{1}H-NMR on a Jeol PMX 60SI spectrometer.

Phenacyl bromide was of commercial quality from freshly opened container. Bromoacetone (**1a**)[20] was prepared by bromination of acetone with bromine. Bromomethyl aryl ketones were prepared by acylation of the appropriate aromatic hydrocarbon with acetic anhydride followed by bromonation with bromine (**1c–e, h–k**)[21-23] or CuBr (**1f**)[24]. Sodium diformylamide (**1**) was prepared by the reported procedure.[15] Chemically pure solvents are used as received.

N,N-Diformylaminoacetone (3a):

A mixture of **1** (11.4 g, 0.12 mol) and bromoacetone (**2a**; 13.7 g, 0.1 mol) in CH_3CN (50 mL) is stirred at r.t. for 2 h. The precipitated NaBr is filtered and washed with CH_3CN (10 mL). The combined filtrates are evaporated and fractionally distilled under reduced pressure; bp 110–125°C/2.7 mbar. Pure product is obtained by refractionation under reduced pressure: yield: 11.2 g (87%); bp 117–120°C/2.7 mbar.

N,N-Diformylaminomethyl Aryl Ketones 3b–j; General Procedure:

A mixture of **1** (11.4 g, 0.12 mol) and the appropriate bromomethyl aryl ketones **2b–j** (0.1 mol) in CH_3CN (50 mL) is stirred at r.t. for

Table. Compounds **3–5** Prepared

Product	Yield[a] (%)	mp (°C) (solvent) or bp (°C)/mbar	Molecular Formula[b] Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR[c] δ, J (Hz)
3a	87	117–120/2.7	$C_5H_7NO_2$ (129.1)	1710, 1650	2.20 (s, 3H, CH_3), 4.53 (s, 2H, CH_2), 9.20 (s, 2H, CHO)
3b	95	140–141 (EtOAc)	140–141[15]	1680, 1590, 1450, 1400	4.77 (s, 2H, CH), 7.00–7.80 (m, $5H_{arom}$), 8.87 (s, 2H, CHO)
3c	95	139–140 (CH_3CN)	$C_{10}H_8BrNO_3$ (270.1)	1690, 1660, 1580, 1395	4.83 (s, 2H, CH_2), 7.83 (d, $2H_{arom}$, $J = 9$), 8.10 (d, $2H_{arom}$), 9.33 (s, 2H, CHO)
3d	93	136–137 (CH_3CN)	$C_{10}H_8ClNO_3$ (225.6)	1670, 1580, 1400, 1350	4.85 (s, 2H, CH_2), 7.65 (d, $2H_{arom}$, $J = 9$), 8.18 (s, $2H_{arom}$, $J = 9$), 9.33 (s, 2H, CHO)
3e	90	127–128 (EtOAc)	$C_{11}H_{11}NO_3$ (205.2)	1670, 1580, 1400, 1350	2.38 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 7.32 (d, $2H_{arom}$, $J = 8$), 8.00 (d, $2H_{arom}$, $J = 8$), 9.20 (s, 2H, CHO)
3f	92	97–98 (EtOAc)	$C_{11}H_{11}NO_4$ (221.2)	1670, 1595, 1570, 1500	3.80 (s, 3H, CH_3), 4.90 (s, 2H, CH_2), 6.85 (d, $2H_{arom}$, $J = 9$), 7.82 (d, $2H_{arom}$, $J = 9$), 8.93 (s, 2H, CHO)
3g	95	89–90 (EtOAc)	$C_{12}H_{13}NO_3$ (219.2)	1670, 1600, 1560, 1490	2.43 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 7.22 (m, $2H_{arom}$), 7.83 (d, $1H_{arom}$, $J = 9$), 9.23 (s, 2H, CHO)
3h	94	111–112 (EtOAc)	$C_{12}H_{13}NO_3$ (219.2)	1680, 1660, 1600, 1560	2.38 (s, 6H, CH_3), 5.13 (s, 2H, CH_2), 7.43 (d, $1H_{arom}$, $J = 9$), 8.00 (m, $2H_{arom}$), 9.37 (s, 2H, CHO)
3i	98	142–144 (EtOH)	$C_{16}H_{13}NO_3$ (267.3)	1690, 1660, 1595, 1400	5.17 (s, 2H, CH_2), 7.43–8.28 (m, $9H_{arom}$), 9.47 (s, 2H, CHO)
3j	88	121–122 (EtOAc)	$C_{14}H_{11}NO_3$ (241.2)	1690, 1660, 1500, 1400	5.22 (s, 2H, CH_2), 7.23–8.40 (m, $7H_{arom}$), 9.47 (s, 2H, CHO)
4a	91	112–115/2	$C_4H_7NO_2$ (101.1)	3200, 1710, 1660	2.17 (s, 3H, CH_3), 4.19 (d, 2H, $J = 5$, CH_2), 8.37 (s, 1H, CHO)
4b	96 (90)[d]	60–61	80–82[12]	3250, 2850, 1690, 1650	4.83 (d, 2H, $J = 5$, CH_2), 7.06 (br, 1H, NH), 7.30–8.10 (m, $5H_{arom}$), 8.30 (s, 1H, CHO)
4c	92 (89)[d]	145–146 (acetone/hexane)	$C_9H_8BrNO_2$ (242.1)	3250, 1690, 1675, 1645	4.85 (d, 2H, $J = 5$, CH_2), 7.03 (br, 1H, NH), 7.77 (d, $2H_{arom}$, $J = 9$), 8.00 (d, $2H_{arom}$, $J = 9$), 8.50 (s, 1H, CHO)
4d	95 (89)[d]	109–110 (acetone/hexane)	$C_9H_8CNO_3$ (197.6)	3250, 1690, 1675, 1650	4.87 (d, 2H, $J = 5$, CH_2), 7.24 (br, 1H, NH), 7.60 (d, $2H_{arom}$, $J = 9$), 8.07 (d, $2H_{arom}$, $J = 9$), 8.50 (s, 1H, CHO)
4e	93 (85)[d]	92–93 (acetone/hexane)	$C_{10}H_{11}NO_2$ (177.2)	3350, 1685, 1660, 1500	2.47 (s, 3H, CH_3), 4.87 (d, 2H, $J = 4$, CH_2), 7.23 (br, 1H, NH), 7.43 (d, $2H_{arom}$, $J = 8$), 8.03 (d, $2H_{arom}$, $J = 8$), 8.53 (s, 1H, CHO)
4f	96 (90)[d]	88–89 (acetone/hexane)	$C_{10}H_{11}NO_3$ (193.2)	3250, 1670, 1640, 1600	3.83 (s, 3H, CH_3), 4.57 (d, 2H, $J = 4$, CH_2), 6.87 (d, $2H_{arom}$, $J = 9$), 7.30 (br, 1H, NH), 7.83 (d, $2H_{arom}$, $J = 9$), 8.10 (s, 1H, CHO)
4g	97 (93)[d]	87–88 (acetone/hexane)	$C_{11}H_{13}NO_2$ (191.2)	3300, 1670, 1640, 1605	2.33 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.60 (d, 2H, $J = 4$, CH_2), 7.00 (m, 3H, $2H_{arom}$ + NH), 7.60 (d, $1H_{arom}$, $J = 9$), 8.20 (s, 1H, CHO)
4h	92 (91)[d]	97–98 (acetone/hexane)	$C_{11}H_{13}NO_2$ (191.2)	3350, 1690, 1660, 1500	2.30 (s, 6H, CH_3), 4.65 (d, 2H, $J = 4$, CH_2), 6.87 (br, 1H, NH), 7.13 (d, $1H_{arom}$, $J = 8$), 7.60 (m, $2H_{arom}$), 8.22 (s, 1H, CHO)
4i	98 (95)[d]	85–86 (acetone/hexane)	$C_{15}H_{13}NO_2$ (239.3)	3300, 1670, 1650, 1600	4.93 (d, 2H, $J = 5$, CH_2), 7.15 (br, 1H, NH), 7.43–8.23 (m, $9H_{arom}$), 8.53 (s, 1H, CHO)
4j	96 (85)[d]	oil	$C_{13}H_{11}NO_2$ (213.2)	3300, 1680, 1655, 1490	4.82 (d, 2H, $J = 5$, CH_2), 6.67–9.00 (m, $9H_{arom}$)
5a	91	70–71 ($EtOH/Et_2O$)	75[16]	3000–2400, 1710, 1290	–
5b	95 (90)[e]	183–184 (*i*-PrOH)	185–186[17]	3200–2300, 1690, 1500	4.83 (s, 2H, CH_2), 4.87 (HDO), 7.63–8.30 (m, $5H_{arom}$)
5c	96 (94)[e]	272–274 (2N HCl)	275[17]	3150–2500, 1670, 1465	4.80 (HDO), 4.93 (s, 2H, CH_2), 8.03 (d, $2H_{arom}$, $J = 9$), 8.43 (d, $2H_{arom}$, $J = 9$)

Table. (continued)

Product	Yield[a] (%)	mp (°C) (solvent) or bp (°C)/mbar	Molecular Formula[b] Lit. mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H-NMR[c] δ, J(Hz)
5d	92 (87)[e]	270–271 (EtOH)	270–271[17]	3150–2500, 1680, 1470	4.93 (HDO), 4.97 (s, 2H, CH_2), 8.20 (d, $2H_{arom}$, $J = 8$), 8.40 (d, $2H_{arom}$, $J = 8$)
5e	98 (93)[e]	205–206 (*i*-PrOH)	206–207[17]	3200–2500, 1680, 1465	2.47 (s, 3H, CH_3), 4.81 (s, 2H, CH_2), 4.84 (HDO), 7.57 (d, $2H_{arom}$, $J = 8$), 8.10 (d, $2H_{arom}$, $J = 8$)
5f	97 (92)[e]	200–201 (EtOH)	200[17]	3150–2500, 1675, 1600	3.93 (s, 3H, CH_3), 4.80 (s, 2H, CH_3), 4.83 (HDO), 7.13 (d, $2H_{arom}$, $J = 9$), 8.10 (d, $2H_{arom}$, $J = 9$)
5g	93 (88)[e]	183–184 ($EtOH/Et_2O$)	$C_{10}H_{14}ClNO$ (199.7)	3200–2500, 1675, 1460	2.48 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 4.80 (s, 2H, CH_2), 4.92 (HDO), 7.50 (m, $2H_{arom}$), 8.03 (d, $1H_{arom}$, $J = 9$)
5h	97 (90)[e]	210–211 ($EtOH/Et_2O$)	213[18]	3200–2500, 1685, 1485	2.23 (s, 6H, CH_3), 4.73 (s, 2H, CH_2), 4.80 (HDO), 7.37 (d, $1H_{arom}$, $J = 9$), 7.83 (m, $2H_{arom}$)
5i	99 (93)[e]	184–185 (2N HCl)	185–186[17]	3100–2500, 1670, 1600	4.83 (HDO), 4.88 (s, 2H, CH_2), 7.43–8.22 (m, $9H_{arom}$)
5j	95 (86)[e]	190–191 (EtOH)	185–186[19]	3200–2300, 1670, 1470	4.87 (HDO), 4.93 (s, 2H, CH_2), 7.80–9.17 (m, $7H_{arom}$)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.27, N ±0.19.
[c] Solvent: $CDCl_3$/TMS for **3a**, **4a–j**; acetone-d_6/TMS for **3b–j**, **4j**; D_2O/DSS for **5a**, **b**, **e–h**; D_2O/DMSO-d_6/DSS for **5c**, **d**, **i**, **j**.
[d] Yield in parenthesis refers to one-pot preparation **2** → **4** based on **2**.
[e] Yield in parenthesis refers to one-pot preparation **2** → **5** based on **2**.

2 h and then heated to ca. 70 °C. The hot mixture is filtered and the solid is washed with hot CH_3CN (20 mL). The combined filtrates are evaporated to ca. 30 mL and allowed to stand undisturbed for thorough crystallization. The crystals are collected by suction filteration and washed with $CHCl_3$ (10 mL) to give **3b–j** in high purity. Analytical samples are obtained by recrystallization from EtOAc. In the case of **3k** it is necessary to recrystallize it directly from EtOAc (Table).

One-Pot Preparation of *N*-Formylaminomethyl Aryl Ketones 4; 4b–j from 2b–j; General Procedure:
A mixture of **1** (1.1 g, 12 mmol) and the appropriate bromomethyl aryl ketone **2b–j** (10 mmol) in EtOH (10 mL) is stirred at r.t. for 2 h and then at 70 °C for 30 min. The cooled mixture is filtered and the solid is washed with EtOH (2 mL). The volume of the combined filtrates is reduced in a rotary evaporator and the remaining residue is redissolved in EtOAc (30 mL), washed with water (2 × 10 mL), dried (Na_2SO_4) and evaporated to give **4b–j**. The crude product is purified either by recrystallization (for **4c–i**) or column chromatography eluting with EtOAc/petroleum ether (bp 60–90 °C) (for **4b,j**).

***N*-Formylaminoacetone (4a):**
A mixture of *N,N*-diformylaminoacetone (**3a**; 12.9 g, 0.1 mol) and KOH (0.5 g) in EtOH (50 mL) is stirred at r.t. for 30 min. The mixture is evaporated and the residue is fractionally distilled; yield: 9.1 g (91 %); bp 112–115 °C/2.7 mbar.

***N*-Formylaminomethyl Aryl Ketones 4b–j from 3b–j; General Procedure:**
A mixture of *N,N*-diformylaminomethyl aryl ketone **3b–j** (10 mmol) and NaOH or KOH (5–10 mg) in EtOH or MeOH (10 mL) is stirred at r.t. for 10 min and then evaporated to dryness under reduced pressure. The residue is washed with water and dried to give pure **4b–j** (Table).

Aminomethyl Aryl Ketone Hydrochlorides 5b–j from Sodium Diformylamide (1) and Bromomethyl Aryl Ketones 2b–j; General Procedure:
A mixture of **1** (1.1 g, 12 mmol) and the appropriate bromomethyl aryl ketone **2b–j** (10 mmol) in EtOH (20 mL) is stirred at r.t. for 2 h and then at 50 °C for 30 min. Thereafter 36 % HCl (2 mL) is added and the mixture is refluxed for 30 min. The solvent and excess HCl are removed under reduced pressure. The residue is heated with EtOH (10 mL) and the insoluble NH_4Cl is rapidly filtered and washed with hot EtOH (2 mL). The combined filtrates are evaporated to dryness under reduced pressure. The crude product is purified by recrystallization. In the case of **5c,i**, the final extraction with EtOH is omitted, the residue is purified by recrystallization from 2 N HCl (Table).

Aminomethyl Ketone Hydrochlorides 5 from *N,N*-Diformylaminomethyl Ketones 3; General Procedures:
5a: A mixture of *N,N*-diformylaminoacetone (**3a**; 1.3 g, 10 mmol) and 5 % HCl/EtOH (25 mL, freshly prepared from 5.4 mL HCl and 60 mL EtOH) is allowed to stand at r.t. for 2 d and then evaporated to dryness under reduced pressure. The residue is washed with Et_2O (10 mL) and dried in a vacuum desiccator (H_2SO_4) to give pure **5a** (Table).

5b,e–i: A mixture of *N,N*-diformylaminomethyl ketones **3b, e–i** (10 mmol) and 5 % HCl/EtOH (25 mL) is allowed to stand at r.t. for 2 d and then Et_2O (25 mL) is added with shaking. The precipitate is collected by suction filtration, washed with Et_2O (5 mL) and dried in a vacuum desiccator (H_2SO_4) to give pure **5b, e–i** (Table).

5c,d,j: A mixture of *N,N*-diformylaminomethyl ketone **3c,d,j** (10 mmol) and 5 % HCl/EtOH (25 mL) is allowed to stand at room temperature for 2 d. The precipitate is collected by suction filteration and washed with EtOH (2 mL) to give pure **5c,d,j** (Table).

5a–j: A mixture of *N,N*-diformylaminomethyl ketone **3a–j** (10 mmol) and 6 N HCl (5 mL) is heated at 120 °C for 30 min and then evaporated to dryness to give pure **5** (Table).

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