Organometallic Addition to *N*-(*N*-Acyl-*N*-methylamino)cycloimminium Salts: A General Method for Ketone Synthesis

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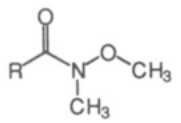
Many methods for the formation of ketones by reaction of organometallics with carboxylic acid derivatives have appeared in the literature.[1] Even though these approaches produced the desired ketones, yields were often low due to the subsequent addition of the organometallic reagent to the ketone to produce tertiary alcohols.

Several groups have employed appropriate carboxylic acid derivatives as selective acylating agents in which the formation of tertiary alcohols is not a problem. These derivatives usually contain a ligand which stabilizes the intermediate formed by chelation, thus preventing premature release of the ketone functionality and avoiding side products from addition of the nucleophile.[3-6] The most effective agents for the direct acylation of unstabilized organometallics appear to be the *N*-methoxy-*N*-methylamides **1** reported by Nahm and Weinreb.[5] These amides react with organolithium and Grignard reagents to produce ketones through a metal-chelated intermediate which is stable up to room temperature.



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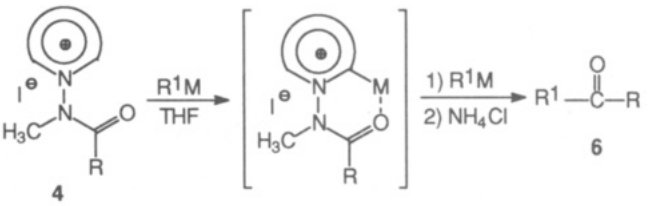
Results and Discussion

In conjunction with a program concerning the development of new synthetic uses for *N*-aminocycloimminium salts,[7] we have discovered that *N*-(*N*-acyl-*N*-methylamino)cycloimminium salts **4** cleanly react with Grignard and organolithium reagents for form ketones in good yields. These acylating agents were prepared from azines or azoles using standard amination procedures. The *N*-amino derivatives **2** were acylated with acyl chlorides, and the resulting betaines **3** formed were alkylated with methyl iodide to give the salts **4**, which show normal amide stability and do not require special handling or storage.

Scheme I



4 **5** **6**

Several points are noteworthy. Experiments with salts **4** showed that addition of 1.0 equiv of *n*-BuLi gave low yields of the corresponding ketones at temperatures between −78 and 20 °C, with the starting material being recovered in high yield after quenching and working up. In contrast, the addition of 2.0 equiv of the organolithium reagent led to ketones in good yield. This result suggested that 1 equiv of the organometallic reagent was consumed in the metalation of the heteroaromatic moiety. To demonstrate this, the salt **4e** was treated with 1.0 equiv of *n*-BuLi at −78 °C followed by quenching with D_2O at room temperature. This resulted in almost complete deuteration of the pyridinium system at the 2-position. Furthermore, when this method of acylation is used, no significant amounts of tertiary alcohols have been detected when excess organometallic reagent (3–10 equiv) was used. We believe that the metalated intermediate **5** probably accounts for the observed lack of overaddition products (Scheme I).

Of the various azinium and azolium salts explored, 3-(*N*-benzoyl-*N*-methylamino)-1-methylimidazolium salts proved to be the most effective with *n*-BuLi as is shown in Table I. On the basis of this result, the 3-amino-1-methylimidazolium mesytilenesulfonate was chosen for transformation into salts **4a–d**. Addition of organolithium and Grignard reagents to **4a–d** afforded a variety of ketones **6** with the yields listed in Table II. In all cases tested the reaction rate with Grignard reagents was very slow at −78 °C but increased rapidly as the reaction mixtures were warmed to room temperature. Reaction of the salts with alkyl- and phenyl-magnesium bromides at −78 °C, followed by quenching after 45 min, yielded no more than 10% of the corresponding ketone, whereas analogous reactions which were allowed to warm to room temperature before quenching gave ketones in good yields. On the other hand, organolithium reagents furnished similar high yields after a 30-min reaction time, regardless of being quenched at −78 or 20 °C.

The complete sequence illustrated for **4a** (Scheme II) also merits comment. In a representative procedure the reaction mixture was quenched with NH_4Cl and partitioned between a mixture of water and diethyl ether. The aqueous layer was extracted with diethyl ether, the ketones **6** being isolated from the combined ethereal phase. From

(1) For reviews, see: (a) Shirley, D. A. *Org. React.* **1954**, *8*, 28. (b) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1.

(2) See *inter alia*: (a) Cardellicchio, C.; Fiandanese, V.; Maechese, G.; Ronzini, L. *Tetrahedron Lett.* **1985**, *26*, 3595. (b) Wattanasin, S.; Kathawala, F. G. *Tetrahedron Lett.* **1984**, *25*, 811. (c) Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, M. K. *Tetrahedron Lett.* **1983**, *24*, 4355. (d) Kikkawa, I.; Yorifuji, T. *Synthesis* **1980**, 877. (e) Owsley, D. C.; Nelke, J. M.; Bloomfield, J. J. *J. Org. Chem.* **1973**, *38*, 901.

(3) Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763.

(4) Meyers, A. I.; Comins, D. L. *Tetrahedron Lett.* **1978**, *19*, 5179.

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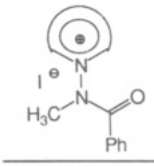
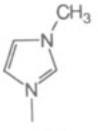
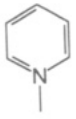
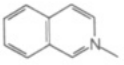
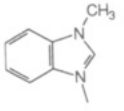
(6) Whipple, W. L.; Reich, H. J. *J. Org. Chem.* **1991**, *56*, 2911.

(7) Most recent works: (a) Carceller, R.; García Navio, J. L.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **1993**, *34*, 2019. (b) Cuadro, A. M.; Valenciano, J.; Vaquero, J. J.; García Navio, J. L.; Alvarez-Builla, J. *Tetrahedron* **1993**, *49*, 3185. (c) Pablo, M.; Gandásegui, T.; Vaquero, J. J.; García Navio, J. L.; Alvarez-Builla, J. *Tetrahedron* **1992**, *48*, 8793.

(8) 1,3-Diphenyl-2-propyn-1-one: Panov, A. M.; Ratayskii, G. U.; Lipovich, T. V.; Filippova, T. M.; Buzilova, S. R. *Zh. Obshch. Khim.* **1982**, *52*, 1761. 1-Phenyl-1-penten-3-one: Covenej, D. J.; Pastel, V. F.; Pattenden, G.; Thompson, D. M. *J. Chem. Soc., Perkin Trans. I* **1990**, *10*, 2721. 1-Phenyl-1-hepten-3-one: Kim, S.; Lee, I. I. *J. Org. Chem.* **1983**, *48*, 2608. 1,5-Diphenyl-1-penten-4-yn-3-one: Умехина, Н. В.; Корхоса, Н. В.; Kasahyesa, B. M.; Cypos, I. H.; Oparas, B. A.; Kopwynos, C. N. *Zh. Obshch. Khim.* **1988**, *58*, 692. 1-(2-Thienyl)pentan-1-one: Friour, G.; Cahier, G.; Normant, J. F. *Synthesis* **1985**, 50. 2-Benzoylthiophene: Klumi, J.; Yoshimuma, K.; Shimada, M.; Kitajima, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 455.

0022-3263/93/1958-5862$04.00/0

Table I. Preparation of 1-Phenylpentan-1-one Using *N*-(N-Benzoyl-*N*-methylamino)cycloimminium Salts and *n*-BuLi

	n-BuLi (equiv)	isolated yield (%)[a]
		
 **4a**	2.1	85
 **4e**	1.0	20
	2.1	70
	10	66
 **4f**	2.1	77
 **4g**	2.1	60

[a] Reactions carried out in THF (5 mL) using 0.5 mmol of the salt at −78 °C and quenched after 45 min.

the aqueous phase the 3-(methylamino)-1-methylimidazolium salt **7** was isolated in high yield by simple removal of the solvent and trituration of the residue with methylene chloride. The crude extract containing the salt **7** when treated with an acyl chloride in a two-phase system regenerated the salt **4a** which was reused in a new reaction cycle without loss of ketone yield.

In summary, the salts **4** can be easily prepared and purified, are stable for long periods of time, and react cleanly with organolithium and Grignard reagents to give ketones in good yields. We think that these salts, and especially **4a**, provide an alternative to previously described acylating reagents. In addition, the resulting *N*-(methylamino)cycloimmium salts produced in the process can be easily recovered and reused.

Experimental Section

General Procedures. All melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity 300 with reference to TMS. Infrared (IR) spectra were obtained as KBr disks on a Perkin-Elmer 1310 spectrophotometer. Microanalyses were performed on an Heraeus CHN Rapid analyzer. Mass spectra were obtained on a Hewlett-Packard 5988 A spectrometer.

All reagents were obtained from commercial sources and used without further purification. THF was distilled from sodium–benzophenone. CH_2Cl_2 was distilled from calcium hydride. Chromatography was performed on silica gel (60 Merck, 230–400 mesh). Solutions of *n*-BuLi and PhLi were titrated as indicated by Watson and Eastham.[9] All reactions involving organometallics were carried out under an argon atmosphere, in glassware that had been dried in 100 °C for at least 3 h. The organometallics reagents were used as 1.6 M solutions in hexane (*n*-BuLi), 2 M in cyclohexane/diethyl ether (7:3) (PhLi), 1 M in THF (PhC≡CLi, PhMgBr) and 3 M in diethyl ether (MeMgBr, EtMgBr).

The following compounds were prepared by known literature procedures: **3-amino-1-methylimidazolium mesitylenesulfonate (2a)**, mp 79–80 °C (lit.[10] mp 79–82 °C); **1-aminopyridinium iodide (2e)**, mp 163–164 °C (lit.[11] mp 163–164 °C); **2-aminoisoquinolinium mesitylenesulfonate (2f)**, mp 134–135 °C (lit.[10] mp 134–135 °C); **3-amino-1-methylbenzimidazolium mesitylenesulfonate (2g)**, mp 218–220 °C (lit.[10] mp 219–221 °C); **1-(benzoylamino)pyridinium hydroxide inner salt (3e)**, mp 179–180 °C (lit.[12] mp 179–180 °C).

Synthesis of Betaines 3. General Procedure. To a mixture of the corresponding *N*-aminocycloimminium salt **2** (4 mmol) and K_2CO_3 (16 mmol) in methylene chloride (40 mL) was added a solution of the acyl chloride (4.8 mmol) in methylene chloride (15 mL) slowly, and the mixture was stirred at reflux temperature for 6 h. The reaction mixture was then filtered, and the solid was washed with methylene chloride (15 mL). The filtrate and the washes were combined and concentrated under reduced pressure. Ethyl acetate was added to the residue whereupon the betaines **3** crystallized on standing.

3-(Benzoylamino)-1-methylimidazolium hydroxide inner salt (3a): white powder from EtOH/EtOAc (83%); mp 159–160 °C (lit.[13] mp 159–160 °C).

3-(Acetylamino)-1-methylimidazolium hydroxide inner salt (3b): white plates from EtOH/EtOAc (65%); mp 158–159 °C (lit.[13] mp 158–159 °C).

3-(Cinnamoylamino)-1-methylimidazolium hydroxide inner salt (3c): brown needles from EtOAc (57%); mp 144–145 °C; IR (KBr) 3142, 1594, 1525, 1350, 717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.6–7.2 (m, 6H), 6.95 (m, 1H), 6.75 (d, 1H, J = 16.1 Hz), 3.86 (s, 3H); MS (EI, 70 eV), m/z 227 (M^+, 100), 226 (98), 131 (32), 124 (32), 103 (35), 88 (41). Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.49. Found: C, 68.41; H, 6.02; N, 18.52.

3-[(2-Thiophenecarbonyl)amino]-1-methylimidazolium hydroxide inner salt (3d): brown plates from EtOAc; yield 63%; mp 178–179 °C; IR (KBr) 3145, 3023, 1566, 1545, 1428 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.51 (t, 1H, J = 1.7 Hz), 7.62 (t, 1H, J = 1.7 Hz), 7.46 (t, 1H, J = 1.7 Hz), 7.41 (d, 2H, J = 4.4 Hz), 6.98 (t, 1H, J = 4.4 Hz), 3.78 (s, 3H); MS (EI, 70 eV), m/z 207 (M^+, 55), 124 (59), 111 (62), 83 (66), 82 (100). Anal. Calcd for $C_9H_9N_3OS$: C, 52.18; H, 4.30; N, 20.27; S, 15.17. Found: C, 51.98; H, 4.50; N, 20.54; S, 15.45.

2-(Benzoylamino)isoquinolinium hydroxide inner salt (3f): yellow needles from EtOH (68%); mp 185–186 °C (lit.[14] mp 186–187 °C).

3-(Benzoylamino)-1-methylbenzimidazolium hydroxide inner salt (3g): white powder from EtOH/EtOAc (83%); mp 180–181 °C (lit.[13] mp 180–181 °C).

Synthesis of *N*-(*N*-Acyl-*N*-methylamino)cycloimminium Salts 4. General Procedure. To a suspension of the corresponding betaine **3** (1 mmol) in ethyl acetate (5 mL, for **3a–c** and **3g**) or acetone (5 mL, for **3d–f**) was added methyl iodide (567 mg, 4 mmol), and the mixture was stirred at room temperature for 24 h (for **3d,e** reflux for 12 h was necessary). The precipitate formed was filtered and recrystallized to give pure salts **4a–g**.

3-(*N*-Benzoyl-*N*-methylamino)-1-methylimidazolium iodide (4a): yellow powder from EtOH; yield 95%; mp 141–142 °C; IR (KBr) 3061, 1683, 1599, 1579, 1477 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (s, 1 H), 8.13 (t, 1 H, J = 1.7 Hz), 7.77 (t, 1 H, J = 1.7 Hz), 7.6–7.4 (m, 5 H), 3.87 (s, 3 H); MS (EI, 70 eV) m/z 142 (22), 105 (100). Anal. Calcd for $C_{12}H_{15}IN_3O$: C, 41.88; H, 4.40; N, 12.21. Found: C, 49.06; H, 4.14; N, 12.50.

3-(*N*-Acetyl-*N*-methylamino)-1-methylimidazolium iodide (4b): white needles from EtOH/EtOAc; yield 88%; mp 150–151 °C; IR (KBr) 3136, 1095, 1701, 1577, 1419 cm^{-1}; ^{1}H NMR

(9) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(10) Tamura, Y.; Minamikawa, J.; Miki, Y.; Matsugashita, S.; Ikeda, M. *Tetrahedron Lett.* **1972**, 4133.

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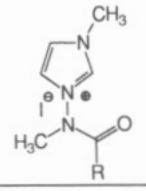
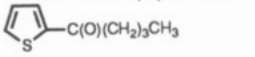
(12) Epsztajn, J.; Lunt, E.; Katritzky, A. R. *Tetrahedron* **1970**, *26*, 1665.

(13) Tamura, Y.; Hayashi, H.; Minamikawa, S.; Ikeda, M. *Heterocycl. Chem.* **1974**, *11*, 781.

(14) Tamura, Y.; Tsjimoto, N.; Uchimura, M. *J. Pharm. Soc. Jpn.* **1971**, *91*, 72.

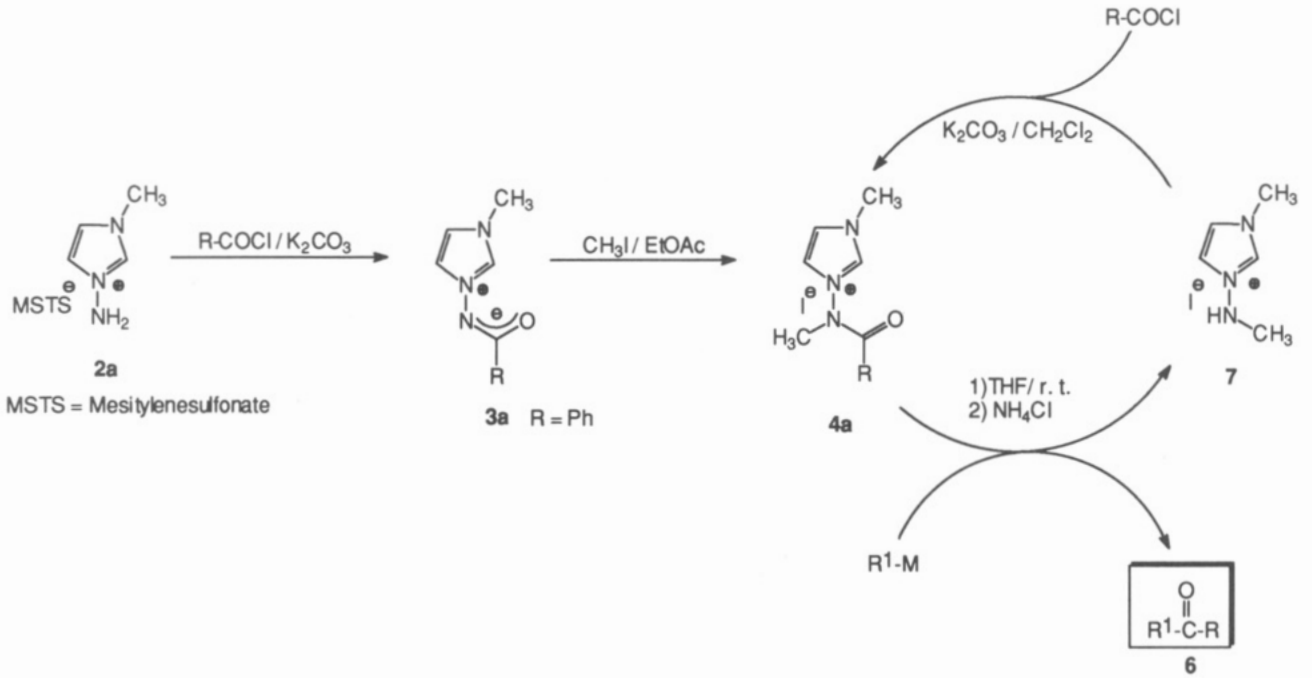
Table II. Preparation of Ketones Using 3-(*N*-Acyl-*N*-methylamino)-1-methylimidazolium Salts and Organometallics



	R^1–M	reactn time (min)	product	isolated yield (%)
4a: R = Ph	CH_3MgBr	45	$PhC(O)CH_3$	85[a]
	CH_3CH_2MgBr	45	$PhC(O)CH_2CH_3$	87[a]
	PhMgBr	60	PhC(O)Ph	75[a]
	PhLi	30	PhC(O)Ph	78[a]
	PhC≡CLi	45	PhC≡CC(O)Ph	80[a]
4b: R = Me	*n*-BuLi	30	$CH_3C(O)(CH_2)_3CH_3$	85[b]
	PhMgBr	60	$CH_3C(O)Ph$	80[a]
4c: R = –CH=CHPh	CH_3MgBr	30	$PhCH{=}CHC(O)CH_3$	85[a]
	CH_3CH_2MgBr	30	$PhCH{=}CHC(O)CH_2CH_3$	81[b]
	n-BuLi	30	$PhCH{=}CHC(O)(CH_2)_3CH_3$	80[b]
	PhMgBr	45	PhCH=CHC(O)Ph	84[a]
	Ph-C≡CLi	45	PhCH=CHC(O)C≡Ph	90[b]
4d: R = 	*n*-BuLi	30		92[b]
	PhMgBr	45		90[b]

[a] Compared to commercially available samples. [b] Compared to authentic samples, see ref 8.

Scheme II



(300 MHz, DMSO-d_6) δ 9.49 (bs, 1 H), 8.01 (bs, 1 H), 7.81 (s, 1 H), 3.90 (s, 3 H), 3.42 (bs, 3 H), 2.06 (bs, 3 H); MS (EI, 70 eV) *m/z* 142 (100), 127 (67), 112 (13), 97 (69). Anal. Calcd for $C_7H_{12}IN_3O$: C, 29.90; H, 4.30; N, 14.95. Found: C, 29.85; H, 4.11; N, 14.69.

3-(*N*-Cinnamoyl-*N*-methylamino)-1-methylimidazolium iodide (4c): white powder from EtOH/EtOAc; yield 92%; mp 184–185 °C; IR (KBr) 3152, 3056, 1662, 1613, 1598 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1 H), 8.09 (s, 1 H), 7.71 (d, 1 H, J = 15.4 Hz), 7.7–7.6 (m, 2 H), 7.58 (s, 1 H), 7.5–7.4 (m, 3 H), 6.70 (bs, 1 H), 3.91 (s, 3 H), 3.55 (bs, 3 H); MS (EI, 70 eV) *m/z* 142 (37), 131 (100), 127 (54), 103 (50). Anal. Calcd for $C_{14}H_{16}IN_3O$: C, 45.54; H, 4.37; N, 11.38. Found: C, 45.59; H, 4.23; N, 11.41.

3-[*N*-(2-Thiophenecarbonyl)-*N*-methylamino]-1-methylimidazolium iodide (4d): brown powder from MeCN/EtOAc; yield 77%; mp 120–121 °C; IR (KBr) 3078, 1652, 1519, 1436, 1412 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, 1 H), 8.19 (t, 1 H, J = 1.8 Hz), 7.95 (dd, 1 H, J = 5.2, 1.2 Hz), 7.88 (t, 1 H, J = 1.8 Hz), 7.3–7.1 (m, 2 H), 3.93 (m, 3 H), 3.51 (s, 3 H); MS (EI, 70 eV) *m/z* 142 (44), 127 (21), 111 (100). Anal. Calcd for $C_{10}H_{12}IN_3OS$: C, 34.40; H, 3.46; N, 12.03; S, 9.16. Found: C, 34.65; H, 3.37; N, 11.97; S, 9.39.

1-(*N*-Benzoyl-*N*-methylamino)pyridinium iodide (4e): yellow plates from EtOH (88%); mp 178–179 °C (lit.[15] mp 178–179 °C).

2-(*N*-Benzoyl-*N*-methylamino)isoquinolinium iodide (4f): yellow needles from EtOH; yield 80%; mp 200–202 °C; IR (KBr) 2993, 1681, 1629, 1442, 1330 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.58 (s, 1 H), 9.18 (d, 1 H, J = 6.9 Hz), 8.80 (d, 1 H, J = 6.9 Hz), 8.55 (d, 1 H, J = 8.5 Hz), 8.5–8.4 (m, 2 H), 8.2–8.1 (m, 1 H), 7.8–7.5 (m, 5 H), 3.75 (s, 3 H); MS (EI, 70 eV) *m/z* 254 (25), 134 (21), 129 (39), 105 (99), 77 (100). Anal. Calcd for $C_{17}H_{15}IN_2O$: C, 52.33; H, 3.87; N, 7.40. Found: C, 52.16; H, 4.10; N, 7.40.

3-(*N*-Benzoyl-*N*-methylamino)-1-methylbenzimidazolium iodide (4g): white needles from EtOH; yield 90%; mp

(15) Katritzky, A. R.; Elison, J. *Gazz. Chim. Ital.* **1987**, *117*, 509.

194–195 °C; IR (KBr) 3018, 1667, 1598, 1556, 1463 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1 H), 8.2–8.0 (m, 2 H), 7.8–7.5 (m, 7 H), 4.14 (s, 3 H), 3.62 (s, 3 H); MS (EI, 70 eV) m/z 142 (31), 105 (100). Anal. Calcd for $C_{17}H_{15}IN_2O$: C, 48.87; H, 4.10; N, 10.68. Found: C, 49.06; H, 4.40; N, 10.92.

Preparation of 4a from 7. A mixture containing 0.26 g (1.08 mmol) of salt 7 and 0.6 g (4.3 mmol) of K_2CO_3 in 5 mL of CH_2Cl_2 was stirred at room temperature for 15 min, and then 0.19 g (1.29 mmol) of benzoyl chloride was added. The resulting mixture was heated at reflux for 6 h. The reaction mixture was worked up as indicated above for the synthesis of **4a** from betaine **3a**. Yield 0.21 g (57%).

Synthesis of Ketones 6. General Procedure. To a solution of the salt 4 (0.5 mmol) in 5 mL of THF at −78 °C was added dropwise the organometallic reagent (1.1 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for the time indicated in Table II. The reaction mixture was quenched with 1 mL of a 1 M solution of NH_4Cl in MeOH: H_2O (1:1) and partitioned between a 1:1 mixture of water and diethyl ether (30 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by passing through a short column (petroleum ether/ethyl acetate, 9:1) gave the pure ketones **6**.

3-(Methylamino)-1-methylimidazolium Iodide (7). Following the general procedure for 1-phenylpentan-1-one from salt **4a**, the aqueous phase was evaporated under reduced pressure and the residue extracted with CH_2Cl_2 (4 × 5 mL). The organic layer was dried over Na_2SO_4 and evaporated to give an oil which was triturated with ethyl acetate. The salt 7 was isolated by filtration and crystallized from EtOH/EtOAc (yellow crystals, 0.95 g, 80%): mp 229–230 °C; IR (KBr) 3180, 3079, 1634, 1570, 1452, 1199, 1037 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1 H), 7.88 (s, 1 H), 7.67 (s, 1 H), 7.16 (q, 1 H, J = 5.6 Hz), 3.29 (s, 3 H), 2.81 (d, 3 H, J = 5.6 Hz); MS (EI, 70 eV) m/z 142 (M^+, 77), 127 (100), 111 (25), 82 (50). Anal. Calcd for $C_5H_{10}IN_3$: C, 25.12; H, 4.22; N, 17.58. Found: C, 25.32; H, 4.46; N, 17.27.

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