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Extension of the Eschweiler-Clarke Procedure to the N-Alkylation of Amides

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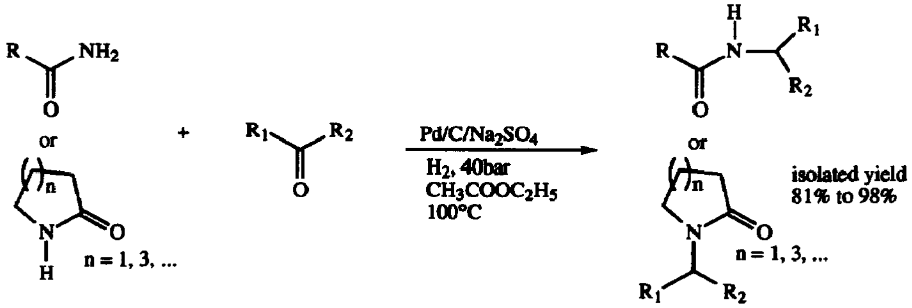
Abstract : The selective N-alkylation of amides (cyclic or acyclic) under hydrogen is reported using aldehydes or ketones as alkylating agents and Pd/C/Na_2SO_4 as catalyst. Good isolated yields are obtained (81% to 98%).

The N-alkylation of amides is an important reaction involved in the synthesis of numerous amines[1]. Interesting methods have been published in the literature which allow selective monoalkylation of primary amides by phase transfer catalysis[2], on inorganic solids[3] or by ruthenium catalysis[4] using alcohols as alkylating agents. Nevertheless, they are inefficient on secondary amides[4] (i.e. cyclic amides) or on compounds with low NH-acidity[2] (i.e. propanamide) and secondary alkylating agents (bromides or alcohols) cannot be used[2] due to the preponderant elimination process.

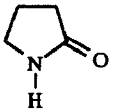
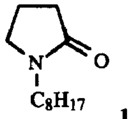
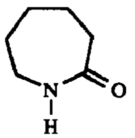
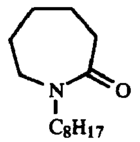
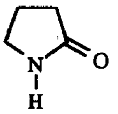
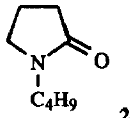
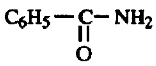
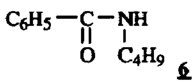
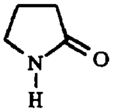
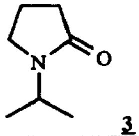
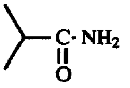
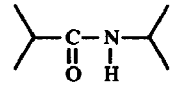
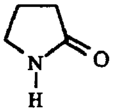
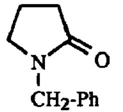
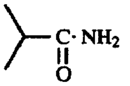
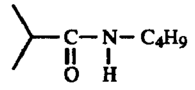
As part of our effort to develop the use of heterogeneous catalysis in fine organic chemistry, we now report a mild and convenient method for the selective mono N-alkylation of primary amides (aromatic or not) and of cyclic amides by modification of the Eschweiler-Clarke procedure[5]. This reaction which allows the reductive alkylation of primary or secondary amines with aldehyde, under hydrogen with Pd/C is reputed to be unefficient on amides. Analysis of the reaction mechanism indicates that the first step (the formation of the acyl imide or acyl iminol) could be the limiting factor of the extension of this reaction to amides.When non protic solvent and Pd/C/sodium sulfate with H_2 pressure were used, reductive alkylation of amides was obtained with good isolated yields (81 to 98%, Table 1)[6]. Cyclic and acyclic (aromatic or not) amides can be used as substrates and both aldehydes or ketones as alkylating agents (Scheme 1).



Scheme 1 : selective N-alkylation of amides using Pd/C/Na_2SO_4.

No O- or C-alkylation product was observed for this versatile and "facile" method which produces no inorganic salt as by product.

Typical procedure: amide (0.01mol), aldehyde or ketone (0.04mol) were dissolved in ethyl acetate (10ml). Then, Pd/C (10%; 0.2mmol) and sodium sulfate (0.01mol) were added. The mixture was stirred at 100°C for 4h under 40bar of hydrogen. After reaction, the solution was filtered off, the solvent evaporated and the product purified by distillation.

Starting Material	Product	Yield % (isolated)	Starting Material	Product	Yield % (isolated)
	 **1**	93		 **5**	96
	 **2**	98	 $C_6H_5-\underset{\overset{\|}{O}}{C}-NH_2$	 $C_6H_5-\underset{\overset{\|}{O}}{C}-\underset{C_4H_9}{\underset{|}{NH}}$ **6**	97[2]
	 **3**	81		 **7**	81*
	 **4**	93		 **8**	89

* reaction time : 48 h

References and notes

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5. March, J.; *Advances in Organic Chemistry*, third Edition, John Wiley and Sons, Inc. : New York 1985; p.p.798-800.

6. All the products were fully characterized : **1** : b.p. 145°C(4mmHg); ^1H NMR (100 MHz, $CDCl_3$) δ [ppm] : 0.9 (m, 3H), 1.4 (m, 14H), 2.2 (m, 2H), 3.3 (m, 4H); ^{13}C NMR (25 MHz, $CDCl_3$) δ [ppm] : 14.4, 18.2, 22.9, 27.2, 27.6, 29.5, 29.6, 31.5, 32.1, 42.8, 47.4, 172.5; M.S. m/z (relative intensity, %) :197 ($M^{+\bullet}$, 14), 126 (16), 70 (28), 41 (34); High resolution : calculated : 197.1779; found : 197.1778. I.R. [cm^{-1}] (neat) : 2906, 1693, 1286. **2** : b.p. 120°C(15); ^1H NMR : 0.9 (m, 3H), 1.3 (m, 6H), 2.1 (m, 2H), 3.3 (m, 4H); ^{13}C NMR : 14, 18.1, 20.3, 29.6, 31.4, 42.6, 47.5, 175.5; M.S. : 141 ($M^{+\bullet}$, 30), 98 (100), 70 (40), 41 (30) ; calculated : 141.1154; found : 141.1153; I.R. : 2916, 1685, 1289. **3** : b.p. 95°C(9); ^1H NMR : 1(d, J = 6.6Hz, 6H, CH_3, 2 (m, 4H), 3.2 (t, J = 7Hz, 2H), 4.2 (m, 1H); ^{13}C NMR : 18.4, 19.8, 21.2, 31.8, 42.1, 42.8, 174.6; M.S. : 127 ($M^{+\bullet}$, 29), 112 (100), 84 (29), 69 (50), 41 (52); calculated : 127.0997; found : 127.0996; I.R. : 2926, 1684, 1288. **4** : b.p. 205°C(6); ^1H NMR : 1.9 (m, 2H), 2.5 (m, 2H), 3.5 (m, 2H), 4.5 (d, J = 21Hz, 2H), 7.6 (m, 5H); ^{13}C NMR : 18.1, 31.8, 41.8, 46.8, 126.4, 127.8, 128.5, 128.7, 176.5 ; M.S. : 175 ($M^{+\bullet}$, 85), 146 (50), 104 (40), 91 (100), 84 (35); calculated :175.0997; found :175.0996; I.R. : 2930, 1694, 720. **5** : b.p. 195°C(8); ^1H NMR : 0.9 (m, 3H), 1.3 (m, 12H), 1.7 (m, 6H), 2.5 (m, 2H), 3.3 (m, 4H); ^{13}C NMR : 14.1, 22.6, 23.5, 26.9, 28.1, 28.7, 29.3, 29.5, 30.1, 31.8, 37.4, 48.3, 49.5, 174.5; M.S. : 225 ($M^{+\bullet}$, 25), 140 (22), 127 (43), 126 (100), 97 (53), 85 (24), 55 (28), 41 (49); calculated :225.2093; found :225.2092; I.R. : 2006, 1646, 1280. **6** : b.p. 202°C(6); ^1H NMR : 0.9 (t, J = 6.6Hz, 3H), 1.5 (m, 4H), 3.4 (m, 2H), 6.2 (m, 1H), 7.4 (m, 3H), 7.7 (m, 2H); ^{13}C NMR : 14, 20.6, 32.1, 40.2, 127.4, 128.8, 131.6, 135.5, 167.9; M.S. : 177 ($M^{+\bullet}$, 18), 135 (32), 105 (100), 77 (73), 51 (20); calculated :177.1154; found :177.1153; I.R. : 3316, 2917, 1644, 1544, 1309, 695. **7** : b.p. 102°C(8); m.p. = 84°C; ^1H NMR : 1.1 (m, 12H), 2.2 (m, 1H), 4 (m, 1H), 5.3 (m, 1H); ^{13}C NMR : 19.8, 22.8, 35.7, 41.1, 176.5; M.S. : calculated : 129.1154; found : 129.1154; I.R. : 3296, 2930, 1652, 1554, 1300. **8** : b.p. 140°C(6); ^1H NMR : 1 (m, 3H), 1.1 (d, J : 7Hz, 6H), 1.3 (m, 4H), 2.3 (m, 1H), 3.3 (m, 2H), 5.5 (m, 1H); ^{13}C NMR : 13.9, 19.8, 20.3, 31.8, 35.7, 39.3, 177.6; M.S. : 143 ($M^{+\bullet}$, 28) , 98 (100), 70 (43), 41 (37); calculated :143.1310; found : 143.1310; I.R. : 3298, 1652, 1557, 1244.

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