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Low-valent Titanium Induced One Pot Syntheses of Imidazolidines

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Abstract: *Under the action of a low-valent titanium reagent, imidazolidine derivatives were synthesized from imines and triethyl orthoformate in moderate yields. NMR spectroscopy was used to assign the configuration of the products.* © 1999 Published by Elsevier Science Ltd. All rights reserved.

Low-valent titanium reagents are versatile reagents in organic synthesis, with high ability for reductive coupling of many functional groups.[1-3] Their application has allowed the synthesis of heterocycles from simple molecules in one step, for example, the reductive cyclization of nitriles to symmetrically substituted tetraalkylpyrazines,[2] and the three molecule reductive cyclization of isothiocyanates to substituted indole-2-carbothioamides.[3] In connection with our interest in investigating new reductive coupling reactions induced by low-valent titanium, we report herein a cross-coupling reaction of imines and triethyl orthoformate, which leads to the formation of imidazolidines.

When a mixture of imine **1** and triethyl orthoformate **2** was treated with low-valent titanium in THF for 50 hours, the cross-coupling product imidazolidine **3** was formed in moderate yield. The reaction intermediate, compound **4**, was also isolated.[4] It was found that the amount of the intermediate, which was isolated, could be reduced by lengthening the reaction time. (Table 1)

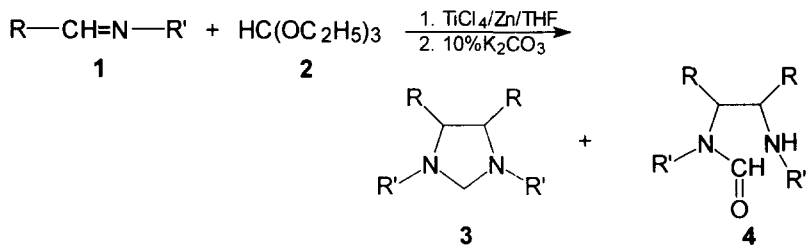

Table 1. The relationship of reaction time and yields (R = R' = C_6H_5)

	Time (h)	Yield of **3a** (%)	Yield of **4a** (%)
1	20	18	24
2	30	32	21
3	50	64	6

The structures of the products **3** were determined from their IR, ^{1}H-NMR and MS spectra and elemental analysis.[4] Different imines led to different isomer distributions of the products in Table 2.

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When one of the isomers is predominant, the pure isomer (**3**-*meso* or **3**-*dl*) can be obtained by recrystallization. We recorded the ^{1}H-NMR spectra of the unrecrystallized products, which were obtained directly by chromatography, to measure the ratio of the two isomers (Table 2).

Table 2. The yields of product **3** and the isomer distributions

	R	R'	Yields(%)	*meso:dl*
a	C_6H_5	C_6H_5	64	20:80
b	C_6H_5	*p*-$CH_3C_6H_4$	53	85:15
c	C_6H_5	*p*-ClC_6H_4	68	10:90
d	C_6H_5	*m*-Cl C_6H_4	47	5:95
e	C_6H_5	*o*-Cl C_6H_4	55	85:15
f	*p*-$CH_3C_6H_4$	C_6H_5	51	95:5
g	*p*-$CH_3OC_6H_4$	C_6H_5	48	85:15
h	*p*-ClC_6H_4	C_6H_5	45	95:5

In conclusion, we have described a new and efficient one-pot coupling and cyclization reaction that furnished imidazolidine derivatives from simple starting materials. Results related to the stereochemistry and complete data will be reported as a full paper.

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4. A general procedure is as follows: A dry 100mL flask was charged with zinc dust (2.60g, 40mmol), $TiCl_4$ (2.20mL, 20mmol) and THF (35mL). The mixture was refluxed for 2 h under argon, then cooled to r. t.. During that time black slurry was formed. A mixed solution of triethyl orthoformate (~3.0g, 20mmol) and imine (**1**, 10mmol) in THF (5mL) was added to the reaction mixture using a syringe, stirred for another 2 h at r.t., then refluxed for 50 h. After removing the THF, the mixture was quenched with 10% K_2CO_3 and extracted with $CHCl_3$ (6×50mL). The organic layer was dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography on silica gel (petroleum ether (60-90°C)) to give imidazolidines.
   Imidazolidine **3b** (*meso*): Mp 141-143°C; ν_{max} (KBr) cm^{-1}: 1610, 1510, 1385, 1270, 810, 790, 690; ^{1}H NMR (500MHz, $CDCl_3$) δ: 6.98-6.53 (m, 18H), 5.62 (d, J=3.0Hz, 1H), 5.10(s, 2H), 4.75 (d, J=3.0Hz, 1H), 2.22(s, 6H); ^{13}C NMR (500MHz, $CDCl_3$) δ: 143.4, 138.3, 129.5, 127.6, 127.4, 126.7, 114.5, 96.1, 70.9, 67.9, 20.4; EI-MS, m/z (%): 404.2 (7.6%), 208.1 (100%), 209.1 (93.4%).
   Imidazolidine **3c** (*dl*): Mp 181-183°C; ν_{max} (KBr) cm^{-1} 1600, 1490, 1450, 1390, 1338, 805, 760, 700; ^{1}H-NMR (60MHz, $CDCl_3$) δ: 7.30-6.45 (m, 18H), 5.34 (s, 2H), 4.82 (s, 2H); EI-MS, m/z(%): 446.2 (9.4%), 444.2 (14.1%), 229.1 (100%), 228.0 (99.0%).
   The intermediate **4a**: Mp 177-178°C; ν_{max} (KBr) cm^{-1}: 3300, 3280, 1660, 1595, 1490, 1280, 745, 700; ^{1}H-NMR (500MHz, $CDCl_3$) δ: 8.40 (s, 1H), 7.45-6.55 (m, 20H), 6.20 (s, 1H), 6.05 (s, 1H), 5.20 (br, 1H, disappeared when D_2O was added); EI-MS, m/z (%): 392.3 (0.8%), 182.1 (100%).