

Bimolecular Self-Condensation of Pyrrolizinones Induced by Grignard Reagent

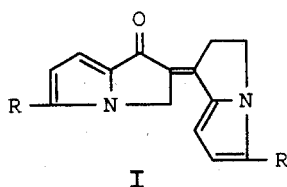
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Abstract: The products of pyrrolizinones with 3-methoxyphenyl magnesium bromide were bimolecular condensation compounds, not the related alcohol, and they were confirmed by IR, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$, HMQC, HMBC, NOE-differ., MS and Elemental Anal.. This indicated that Grignard reagent is a catalyst here.

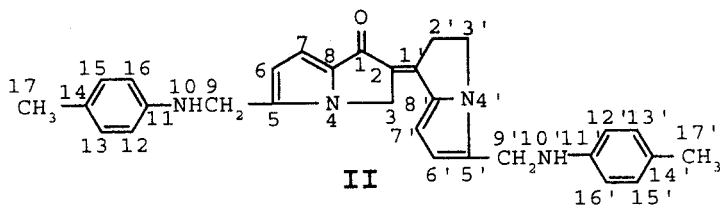
Keywords: Pyrrolizinone, self-condensation, character.

Some 1*H*-2,3-dihydro-1-pyrrolizinones exhibit antiinflammatory and analgesic activities^{1,2}. In search of new biologically active agents, we found that pyrrolizinones did not cause the nucleophilic additive reaction with Grignard reagent under the normal conditions, for example, 3-methoxyphenyl magnesium bromide, but aldol-condensation occurred. The resulting products were bimolecular self-condensation compounds **I**, not the related alcohol. Six target compounds were synthesized and characterized. These compounds also possess some antiinflammatory and analgesic activities.



R=H (33%), 4- CH_3 -PhNHCH₂ (30%), 4-Cl-PhNHCH₂ (34%), 4-Br-PhNHCH₂ (34%), CH_3CO (27%), $\text{CH}_3\text{CH}_2\text{CO}$ (25%)

Taken the example of 5-(4-methylphenylaminomethyl)pyrrolizinone.



To the mixture of 0.4 g (16.66 mmol) magnesium, 8 mL THF and a small grain of iodine, the solution of 2.2 mL (17.46 mmol) 3-bromoanisole in 8 mL THF was added dropwise under nitrogen at room temperature with stirring. Thereafter, the reaction mixture was heated under reflux for 1.5 hours. After cooling to room temperature, the solution of 2 g (8.33 mmol) 5-(4-methylphenylaminomethyl)-pyrrolizinone, in 8 mL THF was added dropwise under vigorous stirring. The reaction proceeded for 5 hours at ambient temperature. Thereafter, 20 mL saturated ammonium chloride solution was added, and extracted with chloroform (3x50 mL). The combined extracts were washed with water, dried, and evaporated to dryness affording 0.7 g of crude **II**. It was crystallized from chloroform. mp 223–224°C, yield 30%.

MS: $m/z=463(M+1)$, Anal. Calcd for $C_{30}H_{30}N_4O$ (462.62): C, 77.89; H, 6.54; N, 12.11. Found: C, 77.98; H, 6.55; N, 11.89. IR: 3250, 2919, 1666, 1603, 1522, 1485, 1439, 1380, 809 cm^{-1} . By spectral analysis (1H -NMR, ^{13}C -NMR, HMQC, HMBC, NOE-differ.), the structure of **II** was confirmed. The NMR data of **II** were listed in Table 1.

Table 1. The NMR data of **II** (in DMSO- d_6)

Carbon No.	δ_c	δ_H	Carbon No.	δ_c	δ_H
1	179.3		1'	136.9	
2	119.9		2'	33.1	3.72(t, J=7.3Hz)
3	46.5	4.85	3'	43.4	4.18(t, J=7.3Hz)
5	133.3		5'	132.8	
6	113.8	6.38(m, J=3.8Hz)	6'	114.7	6.38(m, J=3.8Hz)
7	105.6	6.51(d, J=3.8Hz)	7'	106.2	6.38(m, J=3.8Hz)
8	135.7		8'	134.4	
9	39.9	4.38	9'	38.9	4.26
11	145.9		11'	146.1	
12	112.4	6.59(t, J=8.6Hz)	12'	112.4	6.59(t, J=8.6Hz)
13	129.2	6.90(d, J=7.9Hz)	13'	129.2	6.90(d, J=7.9Hz)
14	124.4		14'	124.4	
15	129.2	6.90(d, J=7.9Hz)	15'	129.2	6.90(d, J=7.9Hz)
16	112.4	6.59(t, J=8.6Hz)	16'	112.4	6.59(t, J=8.6Hz)
17	20.0	2.15	17'	20.0	2.15

NOE-differ. indicated that if 3-H was irradiated, 7'-H peak was increased by 60%. Therefore, the double bond (C=C) of **II** is E-configuration.

The mechanism of above reaction may be the same as aldol-condensation. Thereafter, the aldol-condensations of pyrrolizinone or 5-aminomethylpyrrolizinone were successfully conducted in 10% sodium hydroxide (yield 50-71%).

References

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