

AN UNUSUAL REARRANGEMENT REACTION OF N-ALKYL- α -HALOACETANILIDES
WITH GRIGNARD REAGENTS. A SYNTHESIS OF INDOLE-3-ACETIC ACID

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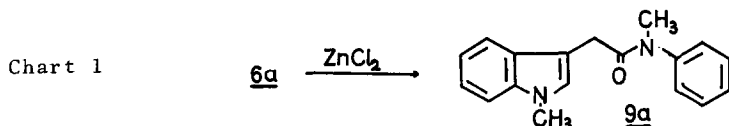
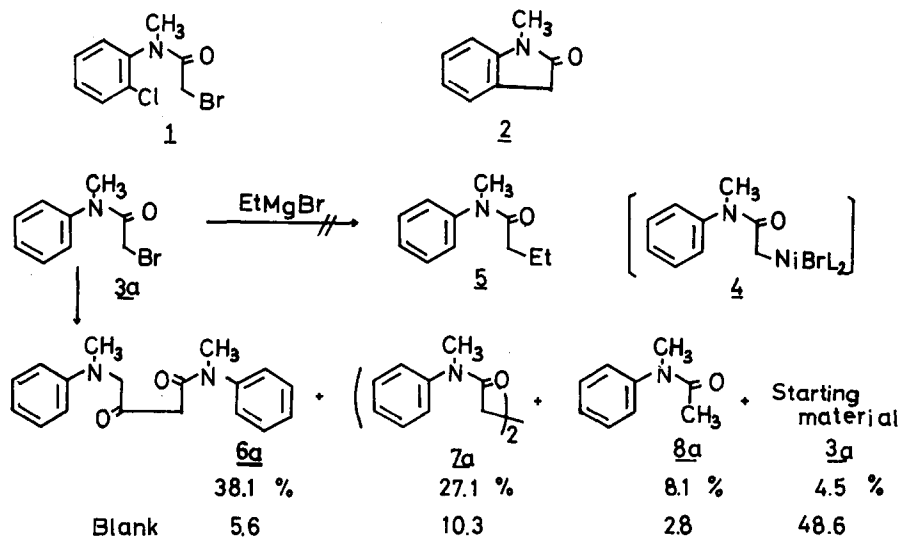
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It has been known that the coupling of alkyl groups by reactions of Grignard reagents and alkyl halides takes place in the presence of transition metal halides.¹ The paper on an elegant work was published by Kumada et al. who demonstrated that the reaction of Grignard reagents with Csp_2 -halides is catalyzed by a dihalodiphosphine nickel to give the cross-coupling products, *selectively*, in very high yields.² With an intention to synthesize the oxindole(2) by an extension of the Kumada's reaction to an intramolecular cross-coupling of organic groups, 2-chloro-N-methyl- α -bromoacetanilide(1) was stirred with Mg ribbon and a catalytic amount of $NiCl_2(PPh_3)_2$ in THF, although the substrate(1) involves a functional group of amide carbonyl being reactive to Grignard reagents. In fact, the expected oxindole(2) was not obtained, and therefore, the reaction was investigated on a simpler system of N-methyl- α -bromoacetanilide[3a, m.p. 45-46.5° (lit.^{3b} m.p. 46.8-47.3°),³ since the halides involving an unsaturated bond at β, γ -positions to the halogen atom are known to be reactive to nickel carbonyl.

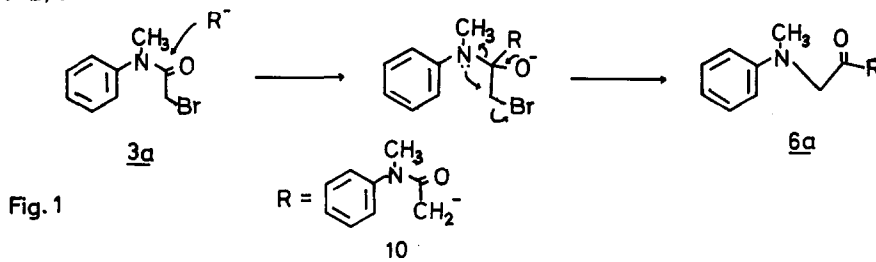
The ethereal solution of 3a and the excess (2.0-2.4 mol. eq.) of EtMgBr containing a catalytic amount of $NiCl_2(PPh_3)_2$ was refluxed for 24 hrs. Contrary to expectation, the cross-coupling product(5), possibly through 4, was not obtained at all, but a basic oil was produced as a major product (38.1%) in addition to the dimeric anilide[7a, m.p. 154-155°, IR ν_{max}^{Nujol} 1630 cm^{-1} , NMR($CDCl_3$) τ 6.76(N- \underline{CH}_3) and 7.65(- \underline{CH}_2 -)] and N-methylacetanilide[8a, m.p. 96-97° (lit.⁴ m.p. 102-104°), M^+ =149, NMR($CDCl_3$) τ 6.72(N- \underline{CH}_3) and 8.11(CO- \underline{CH}_3)] with the starting material(3a). The blank experiment without nickel complex indicates that the catalytic effect of the metal complex is virtually distinct(Chart 1).

The basic oil is positive at $FeCl_3$ test, and indicates the absorptions at

1720 and 1640 cm^{-1} for keto and amide carbonyl groups, respectively. The ultraviolet spectrum ($\lambda_{\text{max}}^{\text{EtOH}}$ 250 and 295 nm) is suggestive of a β -ketoamide structure. Based upon these data, the structure of the product was assigned to 6a, whose nmr spectrum was reconciled to the proposed formula (6a). Furthermore, the β -ketoamide (6a) was heated with zinc chloride without solvent at 120° for 20 min to give the indole-3-acetic acid derivative (9a) in 60% yield according to Julia's procedure.⁵



The formation of this compound (6a) might be explained by attack of the initially formed anion (10) toward the anilide (3a) carbonyl carbon, followed by pursuit of the lone pair of nitrogen to the carbon where the halogen is leaving (Fig. 1).



Similar but different rearrangements were reported on reactions of α -haloketones with Grignard reagents^{6a} and on treatment of a secondary amide with base.^{6b}

The present reaction was very fast in THF as a solvent, and actually proceeded in a moment. Even without $\text{NiCl}_2(\text{PPh}_3)_2$ in this case, the β -ketoanilide (6a) was produced in relatively good yield at 30°. When this reaction was carried out at -10°, the dimeric anilide (7a) was formed in preference to 6a. The effects of substituents on nitrogen and halogen groups to the product ratios were summarized in Table 1.

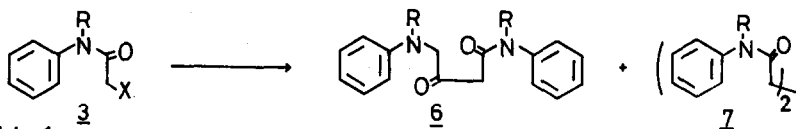


Table 1

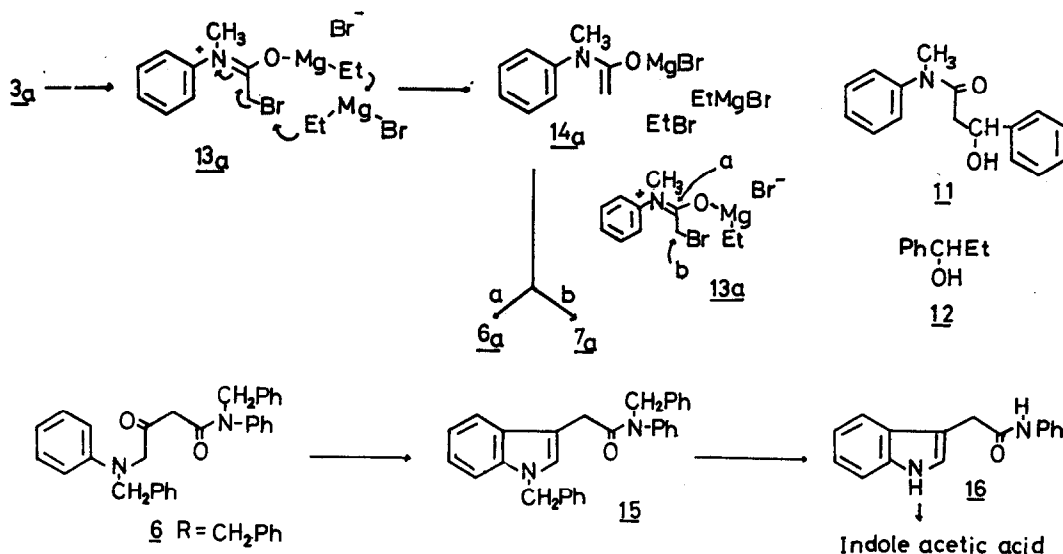
<u>3</u>	R	X	Yield of <u>6</u>	Yield of <u>7</u>
	Me	Br	45.2 %	31.4 %
	Me	Cl	11.8	
	H	Br	0	quant.
	PhCH ₂	Br	48.4	33.4

The compound (6a) was also furnished when 3a was stirred with the excess of PhMgBr or directly reacted with Mg in THF.

Although the exchange of alkyl groups of Grignard reagents with those of alkyl halides does not generally occur in the absence of the transition metal, the present rearrangement proceeded without nickel complex in THF which is known to increase the reactivity of the Grignard reagent. The result might be understood in the following. The substrate (3a) is a reactive α -haloacetanilide, and therefore could be assumed to react with EtMgBr to afford 13a, which may be converted by action of another molecule of EtMgBr into the enamine (14a), being equivalent to the anion (10). The assumption was further substantiated when a 2:1 mol. eq. mixture of EtMgBr and 3a in THF was stirred with benzaldehyde at room temperature for 30 min. to give β -hydroxyanilide (11, m.p. 103.5-105°, $M^+ = 255$) in 52% yield with minor products of 12, 7a and 6a. When 1 mol. eq. of EtMgBr to 3a was used in this reaction, the starting materials were recovered unchanged without formation of 12.

The complex (13a) was attacked at the immonium carbon by the enamine (14a) to

provide the β -ketoanilide (6a) through (a) route. The reaction must have proceeded through (b) route to afford the dimeric product (7a) when 13a was attacked at the halomethylene carbon by 14a.



N-Benzyl- β -ketoanilide (6 R=PhCH₂, m.p. 121-123°, M⁺=448. See Table 1.) was similarly converted to indole-3-acetic acid anilide (15, oil, M⁺=430, UV $\lambda_{\text{max}}^{\text{EtOH}}$ 290 nm), which was debenzylated with sodium in liquid ammonia⁷ to 16 (m.p. 150.5-151.5°, M⁺=250). The anilide (16) was hydrolyzed with 10% hydrochloric acid to give indole-3-acetic acid, m.p. 167.5-169°, which was identical with the authentic specimen (m.p. 164-166°).⁸ Financial support from the Ministry of Education is acknowledged.

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