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A Novel and Efficient Approach to Mono-*N*-Alkyl Anilines *via* Addition of Grignard Reagents to Aryl Azides

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Abstract : Mono-*N*-alkyl anilines were obtained in high yields within a short reaction time when various aromatic azides were reacted with alkyl magnesium halides at room temperature.

Key words : Aryl azides, Alkyl magnesium bromide, Mono-*N*-alkylanilines

Organometallic reagents have become indispensible in organic synthesis and ever since the discovery of the Grignard reaction,[1] new synthetic uses of Grignard reagents have been pursued with sustained interest with a view to explore their scope and applications. Thus Grignard reagents (alkyl and arylmagnesiumhalides) have been successfully utilized for C-C bond formation involving >C=O and C-N multiple bonds[2] adding to functional groups such as aldehydes, ketones, esters, thioesters, imines, hydrazones, nitrile oxides and oxime ethers, isocyanates, nitriles, lactones etc. We report here the addition of various alkyl magnesium bromide reagents to aryl azides which form mono-*N*-alkyl anilines exclusively in high yields. Thus, a number of arylazides were reacted with alkyl magnesium bromide reagents at ambient temperature. All the reactions were performed under moisture free conditions (N_2 atmosphere) using dry diethyl ether (distilled from CaH_2) as solvent. The reaction progress could be monitored by TLC and mono-*N*-alkyl anilines were isolated after an aqueous workup. From the results summarised in the table, the generality of our method is evident as various substituted aromatic azides react with different alkyl magnesium bromide reagents to give good yields of mono-*N*-alkyl anilines. The method works effectively with Grignard reagent bearing both primary and secondary alkyl groups and aliphatic alkyl groups of different chain lengths. It is interesting to note that these transformations lead exclusively to mono-*N*-alkylated anilines and no trace of *N,N*-dialkyl anilines was found in the crude product. This may be attributed to the addition of the Grignard reagent to the azide with successive loss of N_2, followed by proton capture during aqueous workup to form mono-*N*-alkyl anilines. However, addition of aryl magnesium halides gave the corresponding triazine derivatives, which is in conformity with earlier reports on similar reactions.[3] The formation of different products with aryl and alkyl magnesium

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$$Ar-N_3 + R-Mg-X \xrightarrow{\text{Dry ether}} Ar-NH-R$$

Table : Mono-alkylation of aryl azides with alkyl magnesium bromides

entry	Ar	R	Reaction time (h)	Yield (%)[a]	entry	Ar	R	Reaction time (h)	Yield (%)[a]
a.	Phenyl	Ethyl	0.5	90	i.	4-Methoxyphenyl	Isopropyl	1.0	88
b.	ß-Naphthyl	Isopropyl	1.0	88	j.	ß-Naphthyl	Decyl	1.0	88
c.	Tolyl	Ethyl	0.5	89	k.	ß-Naphthyl	Pentyl	1.0	87
d.	Tolyl	Butyl	0.5	87	l.	3,4-Dichlorophenyl	Isopropyl	1.0	85
e.	4-Flourophenyl	Cyclohexyl	1.0	85	m.	3,4-Dimethoxyphenyl	Isopropyl	0.5	87
f.	4-Flourophenyl	Propyl	1.0	82	n.	4-Chlorophenyl	Dodecyl	1.5	85
g.	4-Chlorophenyl	Heptyl	1.0	84	o.	Piperonyl	Propyl	0.5	88
h.	4-Methoxyphenyl	Octyl	0.5	90					

[a] : All products were characterised by IR, ^1H & ^{13}C NMR and Mass spectra and isolated yields are reported, after column chromatography.

bromides may be due to the steric factors, even though this could not be established by experiment.

In conclusion, we have demonstrated a novel and convenient method for the preparation of mono-*N*-alkylated anilines starting from aryl azides. The conversions are clean, high yielding and general with respect to various aryl azides and alkyl magnesium bromide. Even though there are many procedures for the preparation of mono-*N*-alkylated anilines, the majority of such methods[4] require the *N*-alkylation of anilines. Taking note of the difficulties in controlling such *N*-alkylation reactions at the mono-alkyl stage, our method serves as a practical and convenient alternative to currently available methods for the synthesis of these compounds.

References & Notes

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5 In a typical procedure, ethyl magnesium bromide was prepared by stirring magnesium metal (0.36 g, 15 mmol) and ethyl bromide (1.6 g, 15 mmol) in dry-ether (20 ml) for 20 minutes under a N_2 atmosphere at room temperature. This was subsequently added to a solution of phenyl azide (1.19 g, 10 mmol) in dry ether (5 ml). The resulting reaction mixture was stirred at room temperature under a N_2 atmosphere for 30 minutes. After complete conversion, as indicated by TLC, the reaction was quenched with saturated ammonium chloride solution (20 ml) and extracted with ethyl acetate (2 x 25 ml). The combined organic layer was washed with water (2 x 10 ml), brine (20 ml), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to obtain a crude product which was purified by column chromatography on silica gel (Aldrich, 100-200 mesh, ethyl acetate - n-hexane, 1:9) to afford N-ethylaniline (1.09 g, 90%) as pale yellow liquid. ^1H NMR: δ 1.25 (t, 3H, J = 8.0 Hz), 3.15 (q, 2H, J = 8.0 Hz), 3.25 (brs, 1H), 6.5-6.8 (m, 5H). ^{13}C (Proton decoupled, $CDCl_3$) : δ_c 148.2, 128.9, 116.8, 112.5 (Ar), 38.14 (CH_2), 14.5 (CH_3). Mass m/z (%) : 121 (M^+, 40), 106 (100), 77 (30), 51 (15).