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Unorthodox Rate Enhancement in the Mannich Reaction of *Para*-Substituted Phenols Containing Electron-Withdrawing Groups

David A Leigh* and Patrick Linnane

Department of Chemistry
University of Manchester Institute of Science and Technology, PO Box 88, Manchester M60 1QD
United Kingdom

Graham Jackson

Exxon Chemicals Limited, PO Box 1, Milton Hill, Abingdon, Oxfordshire OX13 6BB
United Kingdom

Abstract: *Under classical conditions, the Mannich reaction of most substituted phenols with long chain secondary amines and formaldehyde is dramatically slowed after mono-Mannich base formation. With a powerful electron-withdrawing group in the* para*-position of the phenol, however, further reaction to form the di-Mannich base proceeds in virtually quantitative yields.*

In classical aromatic electrophilic substitution reactions, electron-withdrawing groups tend to *decrease* and electron-donating groups *increase* the rates of reaction. Contrary to these expectations, however, in multiple substitutions involving the Mannich reaction of phenols with long chain secondary amines and formaldehyde (Figure 1), we have found the opposite to be true.

Multiple Mannich base formation of phenols with short chain (C_1-C_4) secondary amines under a variety of conditions is well documented in the literature.[1,2] It was to our surprise, therefore, that we found that although mono-dialkylaminomethylation of many mono-substituted phenols proved facile, a wide range of *ortho*-, *meta*- and *para*-substituted phenols (*e.g.* Me, F, Cl, Br, OMe *etc*) would not efficiently (>10%) undergo a second substitution reaction with long chain (C_8 and higher) secondary amines (*e.g.* Figure 1) even under forcing conditions (*e.g.* refluxing xylene) and after prolonged reaction times (>5 days).[3] In contrast phenols containing powerful electron-withdrawing groups in the *para*-position (*e.g.* CHO, CO_2Me, NO_2, $COCH_3$, CN, CF_3 *etc*) gave virtually quantitative yields (always at least 95%) of the di-substituted Mannich bases under relatively mild conditions (*e.g.* 110°C, toluene) and with short reaction times (4-24h).

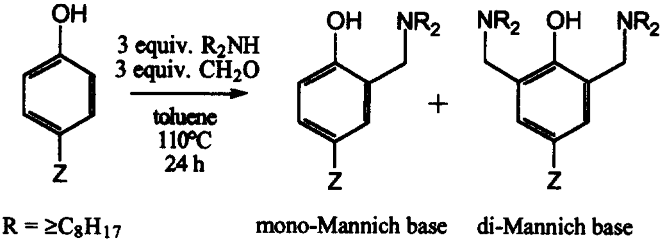

Figure 1. The Mannich reaction of substituted phenols with long chain secondary amines yields mainly either mono- or di- amino-methylated products depending on the nature and position of the substituent on the phenol ring.

Examples of Yields[3] for R = $C_{18}H_{37}$

Z =	*mono-*	*di-*
H	92	08
Me	>98	<02
F	91	09
Cl	95	05
Br	>98	<02
OMe	>98	<02
CHO	<02	>98
CO$_2$Me	<02	>98
NO$_2$	<02	>98
COMe	05	95
CN	<02	>98
CF$_3$	<02	>98

Our initial studies have shown that this effect is not directly related to the acidity of the particular phenols involved[4] and only partially influenced by solvent variations[5]. Further investigations into the details of the mechanism and kinetics of this mechanistic anomaly are ongoing.

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References

(1) Tramontini, M. *Polymer* **1988**, *29*, 771.

(2) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791.

(3) Variations in the molar ratios of reactants, the nature of the formaldehyde source, reaction times and temperatures were carried out leading to the adoption of the following standard conditions for this study: 0.2 mmol phenol, 0.6 mmols amine, 0.6 mmols of paraformaldehyde, 2 ml solvent, reflux for 24 h. With long chain secondary amines (*e.g.* C_8H_{17}, $C_{12}H_{25}$, $C_{16}H_{33}$, $C_{18}H_{37}$, $C_{22}H_{45}$ *etc*) and employing toluene as the solvent, these conditions result in ≥90% yields of mono-Mannich bases when an electron-withdrawing group is not present on the aromatic ring and ≥95% yields of di-Mannich bases when an electron-withdrawing group is *para-* to the phenolic OH. Under identical reaction conditions short chain secondary amines (*i.e.* C_1-C_4) give high yields of the corresponding di-Mannich bases regardless of the nature of the substituents on the phenol ring.

(4) *p*-FC$_6$H$_4$OH and *p*-NCC$_6$H$_4$OH have similar pK_a values yet the former gives mainly mono-substituted products after 12 h reflux in toluene, whereas the latter gives >95% of the di-substituted product under identical conditions.

(5) Polar solvents such as water, ethanol, acetonitrile and ethyl acetate help to promote di-aminomethylation relative to non-polar solvents such as petroleum ether, toluene, xylene and chloroform. However, the difference in relative rates of reaction of the various substituted phenols appears to follow the same trend in each solvent system, *i.e. para*-substituted electron withdrawing groups lead to large (>10^3) rate enhancements in all cases.

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