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A CONVENIENT PREPARATION OF AMINOMETHYL ARYL KETONES AND THEIR DERIVATIVES

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Summary: A convenient preparation of N-phenacyl diformamides, N-phenacyl formamides and aminomethyl aryl ketone hydrochlorides from aryl bromomethyl ketones and sodium diformylamide was described.

α-Aminoketones are important intermidiates of the Knorr pyrrole synthesis[1] and also have considerable values as building blocks for the synthesis of nitrogen-containing heterocycles.[2] Numerous methods of preparing this kind of compound are known and new processes to provide access thereto continue to be devised.[3] Ackrell and Muchowski[3a] have reported a versatile synthesis of α-alkyl α-aminoketones based on α-bromoketones as the starting material. However, this preparation involved four steps starting from α-bromoketones and sodium azide and from requirements of generality, ease of synthesis and the need to prepare a range of derivatives in amounts sufficient for the next reactions, this reported procedure was inadequate. Consequently, we attempted to develop more simple and versatile procedures for preparing a series of aminomethyl aryl ketones and their derivatives. We report here an effective procedure for the preparation of N-protected aminomethyl aryl ketones and aminomethyl aryl ketone hydrochlorides in a single step with excellent yields from aryl bromomethyl ketones and sodium diformylamide.[4]

It was found that various N-phenacyl diformamides 3 were obtained in good yields by treating aryl bromomethyl ketones with sodium diformylamide in acetonitrile at room temperature. However, N-phenacyl formamides 4 were obtained when reactions were carried out in ethanol. The formyl groups of N-phenacyl diformamides 3 can partly be removed by treating 3 with a catalytic amount of sodium or potassium hydroxide in alcohol to give the corresponding N-phenacyl formamides 4. The reason why N-phenacyl diformamides can't be obtained in alcohol is that the sodium diformylamide was contaminated with a small amount of sodium hydroxide. The formyl groups of these compounds can be easily removed by 5% hydrochloric acid in alcohol at room temperature to give the corresponding aminomethyl ketone hydrochlorides 5. The latter can also be obtained in one pot by treating aryl bromomethyl ketones with 2 in ethanol and then with hydrochloric acid.

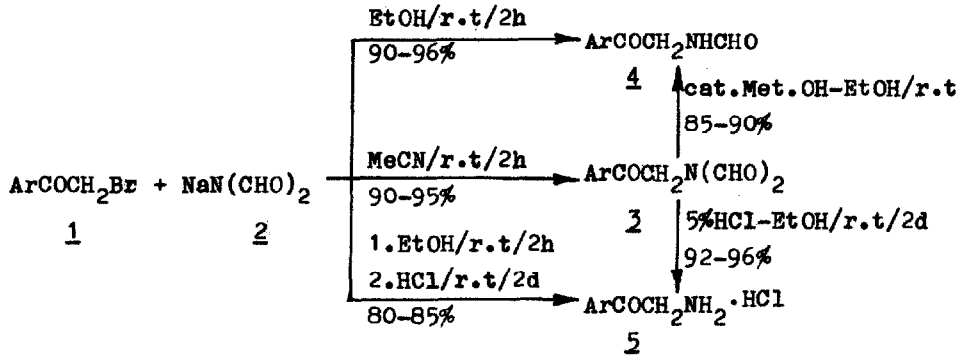

Table: The Yields of N-Phenacyl Diformamides 3 , N-Phenacyl Formamides 4 and Aminomethyl Aryl Ketone hydrochlorides 5 Prepared from Aryl Bromomethyl Ketones 1 and Sodium Diformylamide 2

Ar	Yield% [a]		
	(3)	(4)[b]	(5)[c]
Phenyl-	95	96 (90)	95 (85)
4-Chlorophenyl-	93	95 (89)	96 (82)
4-Bromophenyl-	95	92 (89)	92 (84)
p-Tolyl-	90	93 (85)	94 (80)
4-Biphenylyl-	94	90 (88)	95 (84)

(a) All new compounds gave satisfactory elemental analyses and spectral data. Yield of isolated product. (b) Yield of two step sequence 1→3→4 is given in brackets. (c) Yield of two step sequence 1→3→5 is given in brackets.

Further, it was found that N-phenacyl diformamides are stable in NaH/DMF and undergo no α-C alkylation reactions. However, alkylations took place when N-phenacyl formamides were used to give the corresponding α-alkyl α-formamido ketones. The N-phenacyl diformamides or N-phenacyl formamides can also be alkylated by active alkylating agents in ethanol in the presence of sodium ethoxide. We are exploring the use of N-protected α-aminoketones in synthesis.

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