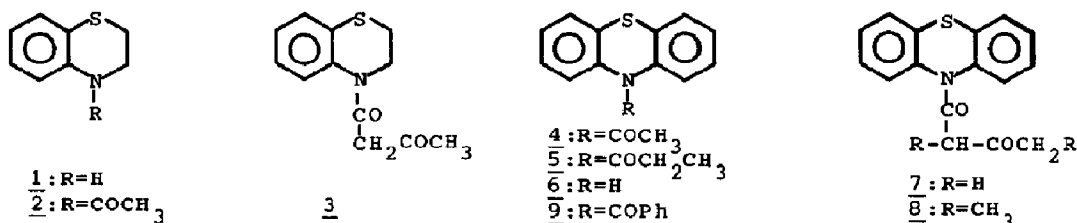


REACTION BETWEEN N-ACYL-2,3-DIHYDROBENZO-1,4-THIAZINE AND N-ACYLPHENOTHIAZINE WITH ORGANOMETALLIC REAGENTS.

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Summary: the title N-acyl-derivatives react with n-BuLi and Grignard reagents leading to products, which, formally, can be considered as derived from a Claisen-type condensation reaction.

As a part of our investigation concerning the synthesis and reactivity of 2,3-dihydrobenzo-1,4-thiazine 1, we have recently discovered that some N-acyl-derivatives of 1 undergo very easy deacylation.¹ The possibility of using these substrates as acylating agents urged us to examine in some detail also the reaction of 2 with organometallics.



Surprisingly we have found that 2 reacts with both n-BuLi and n-BuMgBr leading promptly and with high yield to 1 and the β -dicarbonyl 3, unlike the most di-substituted amides, which, as well known, give ketones,^{2,3} tert-alcohols³ or carbinolamines.⁴

In a typical procedure a solution of the organometallic (1.1 mole) was added dropwise to a stirred solution of 2 (1 mole) under nitrogen. Stirring was continued until the complete disappearance of the starting material (tlc). Then the solution was quenched with NH₄Cl (sat.sol.), the organic layer separated, dried on Na₂SO₄ and the solvent removed in vacuo leaving a residue that was a mixture of two products, which were separated by column chromatography and their structure established by elemental analysis and IR and NMR spectroscopy. Similarly 4 and 5 reacted with the organometallics affording, still cleanly and in high yield, the phenothiazine 6 and the β -dicarbonyls 7 and 8 respectively (see table). This was particularly unexpected, since it is reported that 4 reacts with both Grignards and n-BuLi in a entirely different route, giving the corresponding carbinolamines and a mixture of 2-exanone and di-n-butylmethyl carbinol respectively.^{5,6} It well might be that our choice of the solvent, reactants ratio and experimental conditions are responsible for the discrepancy.

T A B L E

Reaction between N-acyl-2,3-dihydrobenzo-1,4-thiazine and N-acylphenothiazine with organometallic reagents in THF at room temperature.

Compound	Organometallic	Reactants ratio	Reaction time (h)	Condensation Product (yield %) ^a
<u>2</u>	<u>n</u> -BuLi	1:1	16	80
	<u>n</u> -BuMgBr	1:1	1	83
<u>4</u>	<u>n</u> -BuMgBr	1:1	1	90
	PhMgBr	1:1	0.5	90
	<u>n</u> -BuLi	1:1	20	71
	EtMgBr ^b	1:3	1,5	77
	<u>n</u> -BuMgBr	1:1	20	74
<u>9</u>	<u>n</u> -BuMgBr	1:1	16	no reaction

^a Yields represent purified products; ^b The Grignard reagent was prepared in dry ether, the substrate was in ether-THF 1:1.

The nature of the products 3, 7 and 8 suggests that the organometallic, as already reported for some acyl-derivatives⁷, behaves as a base, extracting an α -hydrogen in α -position to the carbonyl; the resulting carbanion, then, presumably attacks the carbonyl carbon of a second molecule of the starting acyl-derivative, leading to the aforementioned β -dicarbonyls, according to a Claisen-type condensation. However, at moment, it is not clear why the compound 9, which does not possess α -hydrogens and was then expected to undergo debenzoylation as a consequence of the nucleophilic attack of the organometallic on the carbonyl (as the carbanion does in the Claisen condensation) did not react at all, at least under the experimental conditions. Therefore we need more evidences to ascertain the real mechanism of the reaction and further experiments are in progress at this end.

This unusual reaction (only N,N-diethylacetamide has been reported⁸ to exhibit a similar behaviour) might be exploited to synthesize new dihydrobenzothiazines and phenothiazines, which are of great interest in the pharmaceuticals area, and the condensation products might mean a viable route to useful β -dicarbonyls.

We thank CNR(Rome) for support.

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(Received in UK 27 May 1980)