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REGIOCONTROLLED ADDITION IN THE REACTION OF N-(α-METHOXYPHENACYL)ANILINES WITH METHYL LITHIOISOBUTYRATE

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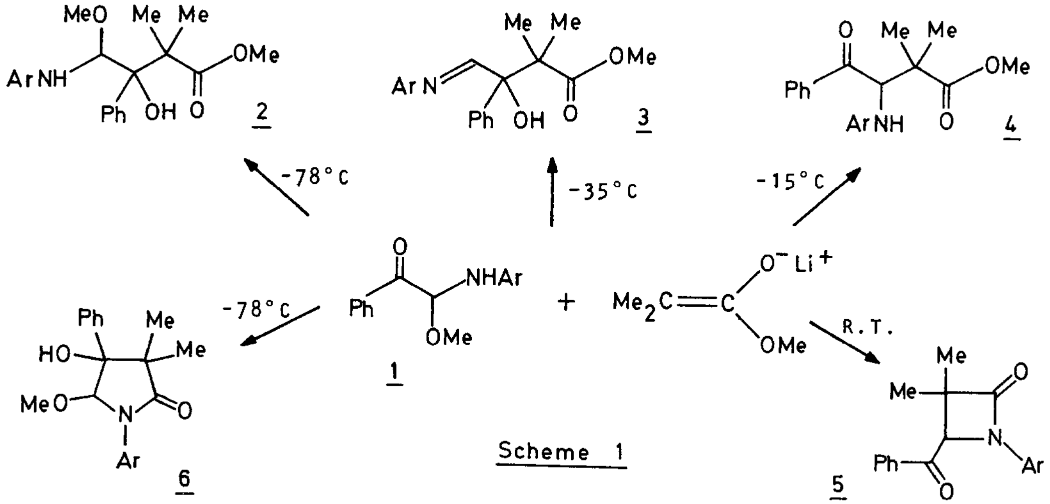
SUMMARY: Reaction of various para-substituted N-(α-methoxyphenacyl)anilines with lithioisobutyrate in excess gives,in good yield, compounds 2-6 through a regiocontrolled process.

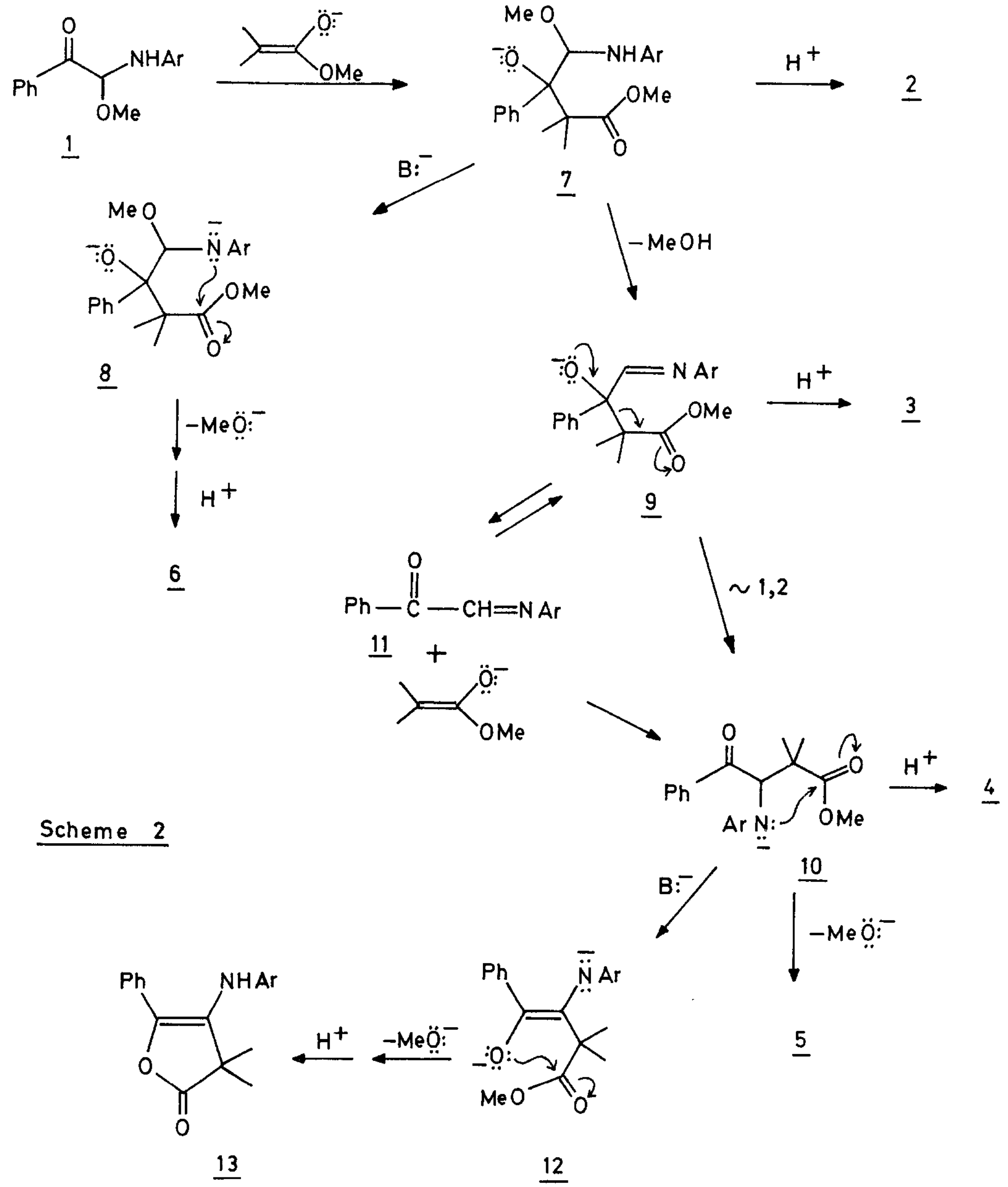
In a previous paper[1], we have reported the synthesis and reactions of some novel substituted β-hydroxy-γ-imino esters which can be easily obtained by reaction of α-iminoketones with lithium ester enolates in a totally site-selective addition to the carbonyl group. In the present communication we report a simple versatile reaction between various para-substituted N-(α-methoxyphenacyl)anilines, 1 (substituent = MeO, Me, H, Br, NO_2)[2], which are synthetic equivalents of the related phenylglyoxal anils, and methyl lithioisobutyrate leading to addition products either to C=O or C=N bonds through a regiocontrolled process[3].



Scheme 1

By reaction of 1 with 2.2 equivalents of methyl lithioisobutyrate[4] we have regiospecifically obtained γ-amino-β-hydroxy-γ-methoxy esters 2[5], β-hydroxy-γ-imino esters 3, β-amino-γ-keto esters 4, β-benzoyl-β-lactams 5 and β-hydroxy-γ-

-methoxy-γ-lactams 6, depending on the nature of the para-substituent and on the experimental conditions (reaction time and temperature) (see Scheme 1)[6]. Isolation, in different experimental conditions, of all these compounds as



Scheme 2

stable products shows clearly the primary course of the whole process (Scheme 2). The reaction starts with the initial addition of the enolate to the carbonyl group to give the alkoxide 7 which, besides yielding 2, can evolve in two ways depending on the nature of Ar. When Ar = p-$NO_2C_6H_4$ the higher acidity of the amine hydrogen (pK_a = 18) allows its capture by a second enolate molecule yielding 8 which cyclises quickly to 6[7]. In the remaining cases this process cannot occur due to the lower acidity of the amine proton[pK_a(aniline) = 25]. Instead demethanolation affording the alkoxide 9 takes place with either formation of 3 or of the amine 10. This can be formed, in turn, either through a process related to the α-ketol rearrangement in the α-hydroxy imine moiety[8], or by reversion to the α-iminoketone 11 and further addition of enolate to its imine group[9,10]. Finally, 10 gives 5 by intramolecular aminolysis at room temperature[11]. When Ar = p-BrC_6H_4, in the isolation of both the β-amino-γ-keto ester 4d and the β-lactam 5d, the aminofuranone 13[12] was obtained as by-product. Its formation might be accounted for through the dianion 12 by intramolecular transesterification.

In conclusion, this reaction becomes a simple method for obtaining in an easy way a variety of interesting polyfunctional compounds.

The detailled study of all the processes implied in this reaction as well as the extension to other N-(α-methoxyaryl)anilines and enolates, including enolates of α-amino esters is now under way.

Acknowledgment.- To Miss M.A. de la Cruz for her colaboration in the preparation of some products.

REFERENCES AND NOTES

1. B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, J. Plumet, and M.M. Sánchez, Tetrahedron Lett., 4403 (1985)
2. These compounds are easily obtained in excellent yield by reaction between phenylglyoxal hydrate and the appropriate amine in refluxing methanol. For the synthesis of these adducts and of the related anils see: (a) B. Alcaide, G. Escobar, R. Pérez-Ossorio, J. Plumet, and D. Sanz, J. Chem. Research, (M), 1466 (1984); (b) M. Prato, U. Quintily, and G. Scorrano, Gazzeta Chimica Italiana, 114, 405 (1984).
3. Proctor et al. have reported the addition of various nucleophiles, such as diethyl sodium malonate to the imino group of the anil from phenylglyoxal and 3,4-dichloroaniline. See, W.R. McKay and G.R. Proctor, J. Chem. Soc. Perkin Trans. 1, 2443 (1981).
4. With lower amount of enolate partial reaction was observed after longer reaction time.
5. Compounds 2 were obtained as a mixture of diastereoisomers in the relative proportions 5:1 in all cases in which analysis of the reaction mixture by ^1H n.m.r. could be achieved (all except when Ar = p-$MeOC_6H_4$). These compounds loose easily methanol in chloroform or methanol solution yielding

quantitatively the related compounds 3. The observed rate of demethanolation depends upon the *para*-substituent (MeO > Me > H > Br). In every case, the major isomer (α), which could be isolated sometimes by crystallization from *n*-hexane, looses methanol much more rapidly than the minor one (β).

6. Experimental conditions for the synthesis of compounds 2-5:
   2a-d: 3 min. at -78°C. Quantitative yield in crude product (by ^{1}H n.m.r.) (see note 5).
   3b-d: 3 min. at -78°C and 75, 90, and 105 min., respectively, at -35°C. Yield: 50-60% (pure product).
   4a-d: 3 min. at -78°C, and 240 (4a-c) and 105 min. (4d) at -15°C. Yield: 70-75% (pure product).
   5a-d: 3 min. at -78°C, and 300, 270, 240 and 45 min., respectively, at room temperature. Yield: 60-70% (pure product).

7. In quantitative yield after 5 min. at -78°C, as a mixture of diastereoisomers in the relative proportion 5:1. The major isomer (α) was easily isolated by crystallization from ethanol, m.p. 158-160°C; i.r. (KBr) ν_{OH} 3440, ν_{CO} 1700 cm^{-1}. When Ar = *p*-MeC_6H_4 occasionally by crystallization of compound 2b from *n*-hexane the related 6b was isolated as by-product, m.p. 134-136°C; i.r. (KBr) ν_{OH} 3430 and ν_{CO} 1700 cm^{-1}.

8. J. March, "Advanced Organic Chemistry: Reactions, Mechanism and Structure", 3rd. ed., Mc Graw Hill, 1985, p. 968.

9. The anil 11 (Ar = *p*-BrC_6H_4) reacts with methyl lithio*iso*butyrate at -78°C for 5 min. yielding the related compond 3 in 75% yield as pure product. Also from 11 the lactam 5d was obtained by using similar experimental conditions to those used for 1. Yield was also similar.

10. Compounds 4 can also be obtained from the related 3 either by treatment with enolate (75% yield) or by refluxing in chloroform.

11. This procedure becomes an alternative route to the synthesis of β-benzoyl-β-lactams by [2+2] cycloaddition of 11 with acyl chloride/Et_3N. See, B. Alcaide, G. Dominguez, G. Escobar, U. Parreño, and J. Plumet, *Heterocycles*, 24, 1579 (1986).

12. White solid, melts with decomposition in a wide range; i.r. (KBr) ν_{NH} 3325, ν_{CO} 1785, and $\nu_{C=C}$ 1655 cm^{-1}; δ(C=O) 179.3.

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