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INFLUENCE OF MAGNESIUM BROMIDE ON THE REGIOSELECTIVITY OF THE CYCLOADDITION OF YNAMINES WITH CYCLENONES : DIFFERENCE IN REACTIVITY BETWEEN CYCLOHEXENONES AND CYCLOPENTENONES.

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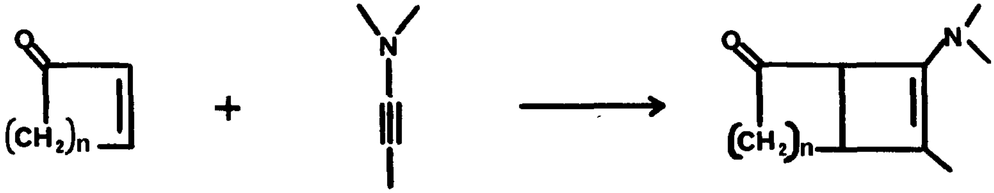
Summary : The cycloaddition of ynamines with cyclohexenones occurs in the presence of magnesium bromide at the carbonyl but proceeds by attack on the carbon-carbon double bond without catalyst whereas, in contrast, with cyclopentenones, the reaction takes place at the carbon-carbon double bond with or without magnesium bromide.

We reported several years ago that reaction of ynamines 2 with cyclenones 1 affords bicyclic enamines of type 3[1]. These enamines, thermodynamically stable when n = 2 or 3[2], are produced in excellent yield when the cyclenone is not very hindered.



1 [n=1,2 and 3] 2 3

We report now our initial results concerning the role of an acid catalysis (namely magnesium bromide) on the regioselectivity of the cycloaddition of ynamines with cyclopentenones and cyclohexenones. These results indeed show the striking difference in the reactivity of the cyclenones depending on their ring size[3].

In the case of a five-membered cyclenone, the presence of magnesium bromide facilitates the cycloaddition and improves the yield by allowing the use of milder conditions[4], but does not change the regioselectivity

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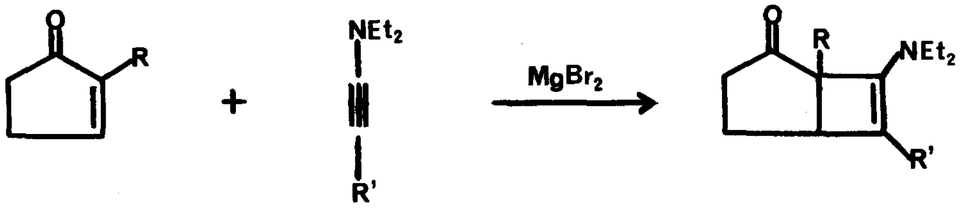
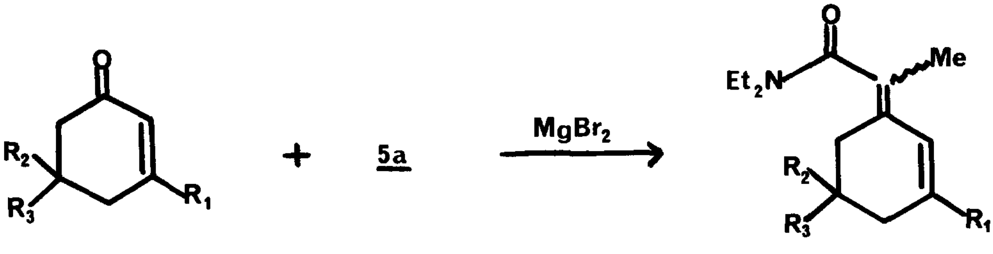
at all. The reaction takes place, with or without magnesium bromide, at the carbon-carbon double bond leading to cycloadducts 6 :



4 5 6

a : R=H ; b : R=Me a : R'=Me ; b : R'=isohexyl

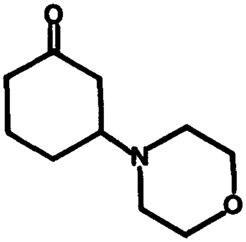
With a six membered cyclenone, the presence of magnesium bromide not only facilitates the reaction of the ynamine but moreover completely reverses its regioselectivity. In this case, reaction does not occur at the carbon-carbon double bond anymore^5 but proceeds by attack on the carbonyle leading to the bis ethylenic amides 8 (mixture of isomers) without any trace of the cycloadduct of type 3.



7 a : $R_1 = R_2 = R_3 = H$; b : $R_1 = R_2 = R_3 = Me$ 8

Thus, for example, the cyclohexenone 7a which, without any catalyst, reacts with 5a to give the corresponding cycloadduct 3, leads, when the reaction is carried out in the presence of magnesium bromide to the bis ethylenic amide 8a : [bp 90°C (0.01 mm) ; UV (ethanol) : λmax 240 nm, (ε 14000) ; IR (neat) : 1640 cm^{-1} ; NMR (CCl_4) δ : 1.10 and 1.15 (2t,J = 8 Hz, 6H), 1.81 (s,3H), 1.7-2.8 (m,9H), 3.38 (m,4H), 5.6-6.5 (m,2H)].

This amide 8a was identified by comparison (IR, NMR, UV) with an authentic sample prepared by elimination of N-methyl morpholine (MeONa, MeOH, 3 h, 65°C) from the ethylenic amide 11. Compound 11 was prepared by reaction of 5a with the carbonyl group of 3-morpholino cyclohexanone 9^6 (9 → 10) followed by methylation (CH_3I, 12 h, 36°C) of 10 (10 → 11).



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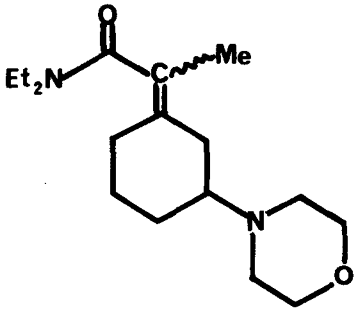

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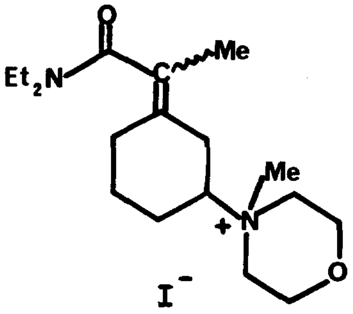

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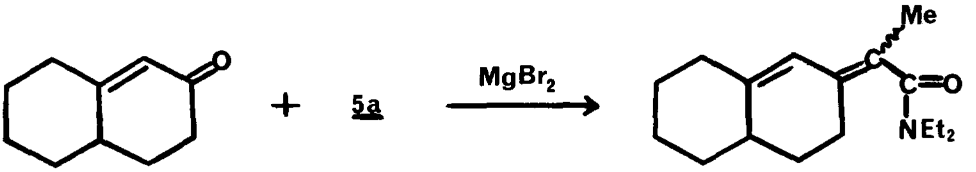
Other examples of the effect of magnesium bromide are found with enones whose carbon-carbon double bond is hindered, such as 7b and the octalone 12. In these cases, the reaction with ynamines takes place without catalyst, by aminovinylation[7] rather than by cycloaddition which would have led to 3. However, under acidic catalysis ($MgBr_2$) the reaction occurs at the carbonyle and affords a 60 to 70 % yield of the bis ethylenic amides 8b and 13.

8b : [bp 100°C (0.05 mm) ; UV (ethanol) : λmax : 249 nm (ε 17300) ; IR (neat) : 1635 cm^{-1} ; NMR (CCl_4) δ : 0.95-1.3 (m,12H), 1.8-2.2 (m,10H), 3.3 (m,4H), 5.75-6.2 (m,1H) ; MS (70 ev), m/e : 249].

13 : [bp 120°C (0.5 mm) ; UV (ethanol) : λmax : 252 nm (ε 20900) ; IR (neat) : 1635 cm^{-1} ; NMR ($CDCl_3$) δ : 1-1.15 (m,6H), 1.8-2.4 (m,12H), 3.38 (m,4H), 5.92 and 6.05 (broad s,2H,mixture of isomers in a ratio 35/65) ; MS (19 ev), m/e : 261].



12 13

It is interesting to note that we have observed this complete reversal of regioselectivity under the influence of a salt coordinating effect only in the case of six membered cyclenones. Thus for example six-membered α,β ethylenic lactames[8] and lactones[9] react with the same regioselectivity in the presence or absence of this catalyst.

References and notes :

1) For a review, see : J. Ficini, Tetrahedron, 32, 1449 (1976).

2) On the other hand, when n = 1, the cycloadduct rearranges in situ : J. Ficini, S. Falou, J. d'Angelo, Tetrahedron Letters, 1931 (1977).

3) a) The influence of a salt coordinating effect has been observed previously during the reduction of cyclohexenones and cyclopentenones : H. Handel, J.L. Pierre, Tetrahedron, 31, 2799 (1975) ; A. Loupy, J.M. Lefour, Tetrahedron, 34, 2597 (1978) ; A. Loupy, J. Seyden-Penne, ibid, (in Press) We thank Drs J. Seyden-Penne and M. Loupy for having informed us of their unpublished results concerning the differences in the reactivity of cyclopentenones and cyclohexenones toward reduction.

   b) The interpretation of this remarkable salt coordinating effect is currently under investigation by Professor Nguyen Trongh Anh and Dr. J.M. Lefour (Université Paris XI, Orsay).

4) For example, the presence of magnesium bromide permits the cycloaddition of 4b and 5b to occur in 70 % yield in 15 mn instead of in 55 % yield after 19 h at 100°C. The general procedure for the reaction of 4 with 5 in the presence of magnesium bromide is as follow : a solution of the ynamine 5 in dry THF is added dropwise under nitrogen to a solution of ketone 4 and $MgBr_2$, previously prepared in THF, at 25°C, from dibromoethane and magnesium turnings (the concentration of ynamine 5 is 1M at the end of the addition). After the required time for reaction the solution is cooled to 0°C and the magnesium bromide rapidly precipitated by addition of mixed solution of ammonium chloride and ammonia. After drying, distillation affords a 70 % yield of the cycloadducts 6. The reaction time is directly dependent of the amount of $MgBr_2$ used : 15 mn with 1 eq., 1 h with 0.5 eq. and 2 h with 0.2 eq. For the reaction of 4a with 5a without any catalyst, see : J. Ficini, A. Krief, Tetrahedron Letters, 1431 (1969).

5) For cycloaddition of ynamines with cyclohexenones, see : J. Ficini, A.M. Touzin, Tetrahedron Letters, 2093 (1972) ; J. Ficini, A.M. Touzin, ibid, 15, 1447 (1974) ; J. Ficini, A. Eman, A.M. Touzin, ibid, 679 (1976).

6) R. Fuks and H.G. Viehe, Chem. Ber., 103, 564 (1970).

7) J. Ficini, J. d'Angelo, C.R. Acad. Sc. Paris, 276, 803 (1973).

8) J. Ficini, A. Guingant, J. d'Angelo, J. Amer. Chem. Soc., 101, 1318 (1979).

9) J. Ficini, L. Duranel, J. d'Angelo, A. Guingant, unpublished results.

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