Tetrahedron Letters, Vol.22, No.26, pp 2487 - 2490, 1981
Printed in Great Britain

0040-4039/81/262487-04$02.00/0

A ONE-STEP SYNTHESIS OF 2,6-DISUBSTITUTED ANILINES FROM ALIPHATIC COMPOUNDS

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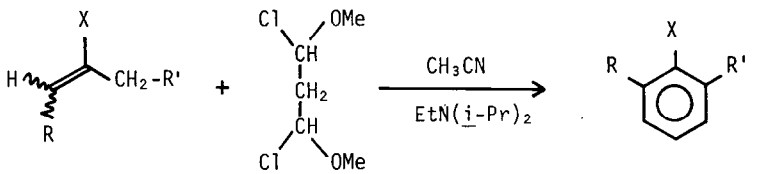
Abstract.- A one-step synthesis of 2,6-disubstituted anilines by reaction of enamines derived from acyclic ketones of the type RCH_2COCH_2R' and 1,3-dichloro-1,3-dimethoxypropane is described.

We have recently described the preparation of 2,4-dialkoxybicyclo[3.2.1]octan-8-ones[1] and 2,4-dimethoxybicyclo[3.3.1]nonan-9-ones[2] by condensation of the appropriate 1,3-dichloro-1,3-dialkoxypropane with N-(cyclopent-1-en-1-yl)pyrrolidine and N-(cyclohex-1-en-1-yl)pyrrolidine, respectively. We describe in this communication a medium yield preparation of 2,6-disubstituted anilines by reaction of enamines[3] derived from acyclic ketones of the type RCH_2COCH_2R' with 1,3-dichloro-1,3-dimethoxypropane[4].



1, X = N- , R = R' = Me

2, X = N- , R = R' = Ph

3, X = N- , R = R' = Ph

4, X = O N- , R = R' = Ph

5, X = N- , R = R' = -COOMe

6, X = N- , R = R' = -COOMe

7, X = O N- , R = R' = -COOMe

8 **8a**, X= N- , R = Me, R' = n-Pr

8b, X= N- , R = n-Pr, R' = Me

9, X = N- , R = R' = Me

10, X = N- , R = R' = Ph

11, X = N-, R = R' = Ph

12, X = O N- , R = R' = Ph

13, X = N- , R = R' = -COOMe

14, X = N- , R = R' = -COOMe

15, X = O N- , R = R' = -COOMe

16, X = N- , R = Me, R' = n-Pr

Scheme 1

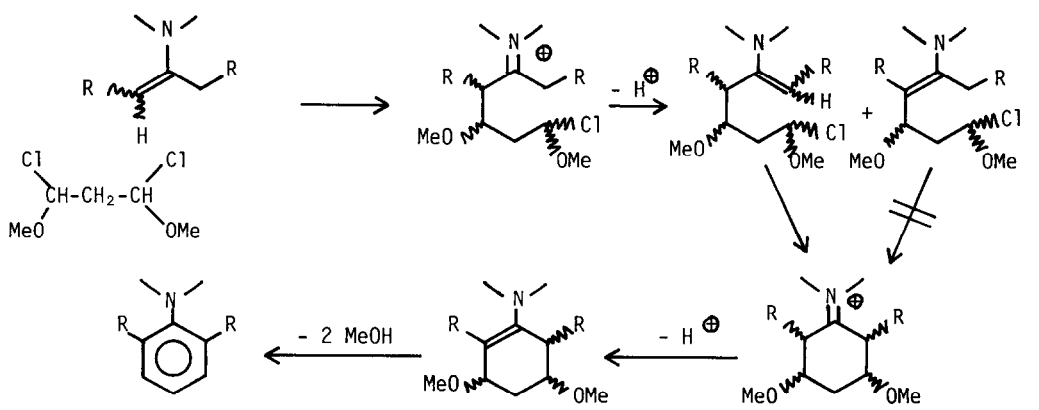
Enamine	Equiv. EtN(isoPr)	Temp.	Time	Aniline	Yield
1	2,5	100°C	16h	9	38,2%[a]
2	2	100°C	16h	10	52,0%[b]
3	2	100°C	16h	11	54,0%[b]
4	2	100°C	16h	12	52,5%[b]
5	1	room	65h	13	31,3%[b]
5	0	room	65h	13	24,5%[b]
6	0	room	65h	14	32,4%[c]
7	0	room	65h	15	29,6%[b]
8	2,5	100°C	16h	16	28,4%[c]

Table 1.- Optimum reaction conditions and yields for the reaction of enamines derived from acyclic ketones of the type RCH_2COCH_2R' and 1,3-dichloro-1,3-dimethoxypropane. a) Yield of chromatographed and distilled product. b) Yield of chromatographed and crystallized product. c) Yield of chromatographed product.

Scheme 2 shows a mechanistic explanation of this reaction. The imonium salt formed after the second alkylation step may lose a proton and methanol to give the aniline. The success of these reactions depends on the ability of the imonium salt formed after the first alkylation step to generate a new enamine by losing a proton from the non-alkylated α-position, and in some of these reactions, this is favoured by using the bulky base ethyldiisopropylamine.

The differences in the observed optimum reaction conditions, specially the equiv. of $EtN(isoPr)_2$, must be related with the acidity of the α-protons of the intermediate imonium salts and the mechanism of methanol elimination. Thus, for R, R' = alkyl or aryl, the best results are obtained by using 2,5 or 2,0 equiv. of $EtN(isoPr)_2$ respectively. However, for R=R'= -COOMe, no $EtN(isoPr)_2$ is needed (see Table 1).

It should be pointed out that a small increase in the yield of 13 was observed using 1 equiv. of $EtN(isoPr)_2$ (see Table 1). However, under these reaction conditions, the yield of 14 and 15 is drastically reduced. The relative stabilities of the enamines 5, 6 and 7 vs bases



Scheme 2

SPECTROSCOPIC DATA

COMPOUND	60 MHz ^{1}H NMR (Solvent)(δ scale)	MS, 70 eV, m/e (%)	M.p. or B.p.(oven)
Dimethyl (E)-3-(N-pyrrolidinyl) pent-2-enedioate, 6.	($CDCl_3$), 4,63(s, 1H), 4,18(s,2H), 3,73(s,3H), 3,60(s,3H), 3,32(m, 4H), 1,95(m,4H).	227(M^+,9), 196(M^+-MeO,26), 168(M^+-CO_2Me,100), 157(M^+-C_4H_8N,25), 70 ($C_4H_8N^+$,81), 59(CO_2Me^+,45).	170-180°C/5 Torr
Dimethyl (E)-3-(N-morpholinyl) pent-2-enedioate, 7.	($CDCl_3$), 5,00(s,1H), 4,22(s,2H), 3,75(m), 3,75(s), 3,63(s) total 10H, 3,23(m,4H).	243(M^+,5), 212(M^+-MeO,12), 184(M^+-CO_2Me,36), 86($C_4H_8NO^+$,40), 59(CO_2Me^+, 100).	166-170°C/0.5 Torr
N-(2,6-dimethylphenyl) pyrrolidine, 9.	($CDCl_3$), 7,09(s,3H), 3,21(m,4H), 2,27(s,6H), 1,99(m,4H).	175(M^+,78), 174(M^+-1,100), 160(M^+-Me,9), 146(M^+-C_2H_5,47), 132(M^+-C_3H_7, 75).	80-84°C/14 Torr
N-(2'-m-terphenyl)pyrrolidine, 10.	($CDCl_3$), 7,50-7,00(m,13H), 2,65 (m,4H), 1,43(m,4H).	299(M^+,98), 298(M^+-1,100), 270(M^+-C_2H_5,11), 256(M^+-C_3H_7,25).	94-95,5°C
N-(2'-m-terphenyl)piperidine, 11.	(CCl_4), 7,30(s,10H), 7,05(s,3H), 2,49(m,4H), 1,10(m,6H).	313(M^+,70), 312(M^+-1,100), 284(M^+-C_2H_5,6), 270(M^+-C_3H_7,10), 256(M^+-C_4H_9,90).	115-117°C
N-(2'-m-terphenyl)morpholine, 12.	(CCl_4), 7,28(s,10H), 7,05(s,3H), 3,08(m,4H), 2,46(m,4H).	315(M^+,33), 314(M^+-1,13), 284(M^+-CH_3O,3), 270(M^+-C_2H_5O,7), 256(M^+-C_3H_7O, 100).	164-165°C
Dimethyl 2-(N-pyrrolidinyl) isophtalate, 13.	(acetone,d-6), 7,70, 7,55, 6,95, 6,82, 6,80, 6,68(AA'B system,3H), 3,85(s,6H), 2,70(m,4H), 1,35(m,4H).	263(M^+,18), 262(M^+-1,5), 248(M^+-CH_3, 100), 232(M^+-MeO,17).	77-78,5°C
Dimethyl 2-(N-piperidinyl) isophtalate, 14.	($CDCl_3$), 7,65, 7,52, 7,18, 7,07, 7,04, 6,92(AA'B system, 3H), 3,90 (s,6H), 3,05(m,4H), 1,60(m,6H).	277(M^+,11), 276(M^+-1,4), 262(M^+-CH_3, 100), 246(M^+-MeO,15).	62-64°C
Dimethyl 2-(N-morpholinyl) isophtalate, 15.	($CDCl_3$), 7,65, 7,53, 7,25, 7,13, 7,10, 7,00(AA'B system,3H), 3,90 (s,6H), 3,83(m,4H), 3,10(m,4H).	279(M^+,9), 278(M^+-1,2), 264(M^+-CH_3, 24), 248(M^+-CH_3O,13), 236(M^+-C_2H_5O, 19), 220(M^+-C_3H_7O,30), 174(100).	95-97°C
N-(2-methyl-6-n-propylphenyl) pyrrolidine, 16.	($CDCl_3$), 7,00(s,3H), 3,15(m,4H), 2,60(m,2H), 2,22(s,3H), 2,10-1,3 (complex, 6H), 0,95(t, 3H).	203(M^+,100), 202(M^+-1,93), 188(M^+-CH_3,20), 174(M^+-C_2H_5,36), 160(M^+-C_3H_7,43)	126-130°C/13 Torr

IR spectra are not significative.
All compounds have correct analytical data.

may be related with this fact, and it may also be related with the fact that, although enamine 5 could be prepared in a standard way from dimethyl 3-oxoglutarate and pyrrolidine, it was not possible to prepare 6 and 7 by this procedure. These enamines were prepared by addition of the corresponding secondary amine to dimethyl allene-1,3-dicarboxylate[5], that to the best of our knowledge, is the only described method to prepare enamines formally derived from dimethyl 3-oxoglutarate.

The method described herein represents an easy entry into 1,2,3-trisubstituted benzenes, not readily available from other benzene derivatives. Moreover, the method might be used for the synthesis of more substituted benzenes by using the appropriate 1,3-dichloro-1,3-dimethoxy derivatives. Alternatively, they could be prepared from the 2,6-disubstituted anilines.

ACKNOWLEDGMENT.- A grant from F.P.I., Ministerio de Educación y Ciencia, to C. Jaime is gratefully acknowledged. We thank M. Guerra from Instituto de Química Bioorgánica (C.S.I.C.) Barcelona, for elemental analysis.

REFERENCES AND NOTES.

1.- P. Camps and C. Jaime, Tetrahedron, 36, 393 (1980).

2.- P. Camps and C. Jaime, Org. Magn. Res., 14, 177 (1980).

3.- Enamines 1, 2, 3 and 4 are known compounds and were prepared by the standard procedure. Enamine 6 was prepared as described by E. Winterfeldt et al. (ref. 5). Enamines 5 and 7 were prepared by the same procedure. Alternatively, 5 was prepared by the standard method. The reaction of 3-heptanone with pyrrolidine under the conditions described by G. Stork et al., J. Amer. Chem. Soc., 85, 207 (1963), for the preparation of enamine 1, yielded 36,7% of a mixture of enamines 8a and 8b, in which 8a seems to be the major component (^{1}H NMR)

4.- General procedure for the synthesis of 2,6-disubstituted anilines:
To a cold solution (ice bath) of 30 mmole of the enamine and the required amount of $EtN(i\text{-}Pr)_2$ (see Table 1) in 30 ml anh. CH_3CN under N_2 atmosphere, 30 mmole of 1,3-dichloro-1,3-dimethoxypropane are slowly added with stirring. The reaction mixture is stirred at room temperature or heated at reflux for several hours (see Table 1). Water (50 ml) is added and the mixture extracted with ether. The crude product is chromatographed on SiO_2 (10 g SiO_2/ g subs.) and crystallized or distilled.

5.- E. Winterfeldt and M. Nelke, Chem. Ber., 101, 2381 (1968).

(Received in UK 27 April 1981)