HETEROCYCLES, Vol 27, No. 10, 1988

REGIOSELECTIVITY IN THE VILSMEIER-HAACK REACTION OF N-BENZYL-1,2,3,4-TETRAHYDROCARBAZOLE[1]

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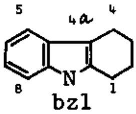
Abstract——The Vilsmeier-Haack reaction of N-benzyl-1,2,3,4-tetrahydrocarbazole (1) with various N,N-disubstituted formamides (6) and phosphorous oxychloride took place not only on the alicyclic portion but also on the benzene moiety depending on the reactivity and bulkiness of the reagents. It was also shown that N-methylformanilide (6e) is the most reactive reagent among 6.

We reported[2] that the Vilsmeier-Haack reaction[3] of N-benzyl-1,2,3,4-tetrahydrocarbazole (1, N-benzyl-THC) with phosphorous oxychloride ($POCl_3$)/N,N-dimethylformamide (DMF) gave the 1-formyl derivative (2) at 0°C and fully aromatized aldehydes (3 and 4) at 120°C. In the earlier paper[2] we described the successful conversion of the aromatized aldehyde (3) to olivacine and suggested the mechanism of the formation of 2, 3, and 4 *via* an intermediate (5). To obtain further confirmation for the suggested mechanism and to improve the yield of the synthetic intermediate (3), we reinvestigated the reaction of 1 with various N,N-disubstituted formamides (6) in place of DMF. We report here that the use of various formamides caused N-benzyl-THC (1) to react with different regioselectivity.

The Vilsmeier-Haack reaction of 1 (1 eq.) with five kinds of N,N-disubstituted



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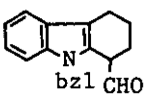

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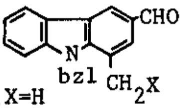
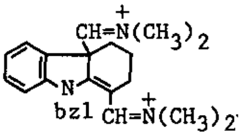


3, X=H

4, X=$N(CH_3)_2$



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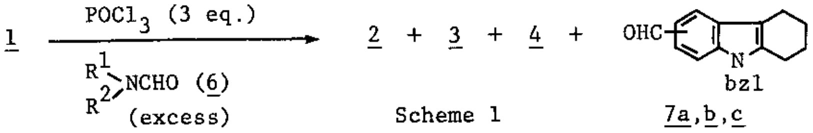
formamides (6a-e) (an excess amount which served as both reagent and solvent) and $POCl_3$ (3 eq.) was carried out at 0 or 120°C (bath temperature), and the results are summarized in Table 1. All products were mono-formyl compounds. In the reaction at low temperature the reagents prepared from smaller formamides (6a-c) gave the 1-aldehyde (2) (runs 1-3), whereas the one prepared from N-methylformanilide (6e) gave a mixture of the aromatic aldehydes (7) (run 5). The yield of 2 decreased with increasing bulkiness of 6 used. At 120°C the reagents prepared from smaller formamides (6a-c) gave mainly the fully aromatized aldehydes (3 and 4) (runs 6-8), the formation of which is closely related[2] to that of the 1-aldehyde (2), whereas larger formamides (6c-e) gave a mixture of the aromatic aldehydes (7) in increasing yield with increasing bulkiness (runs 8-10). The mixture of 7 was separated by column chromatography into three formyl compounds, the 5-, 6-, and 7-aldehydes (7a, 7b, and 7c). The structure of 7b was determined by an alternative synthesis and 7a,c were characterized by elemental analyses and spectral data. The ratio of the yields of 7a,b,c was almost the same in all cases, 7c being the main product. These results can be explained as follows. Vilsmeier-Haack reagents prepared from smaller formamides (6a-c) initially attack the most electron-enriched 4a-position to form an intermediate corresponding to 5, which results in the formation of the 1-aldehyde (2) at 0°C, and the fully aromatized aldehydes (3 and 4) at 120°C.[2] The reagents prepared from larger formamides (6d,e), however, do not attack or have difficulty in attacking the crowded 4a-position both at 0 and 120°C due to their bulkiness. This may be why larger formamides give neither the 1-aldehyde (2) at 0°C nor the fully aromatized aldehyde (3 and 4) at 120°C. The fact that the reagent prepared from N-methylformanilide (6e) easily attacked the electron-poorer benzene moiety rather than the electron-richer 4a-position, should be attributed to its bulkiness and much more enhanced reactivity[3] than the reagents prepared from other formamides (6). In contrast, the reagent prepared from N,N-diisopropylformamide (6d) was not reactive toward either site since it had the same reactivity as formamides 6a-c and bulkiness similar to 6e.



Scheme 1

Table 1. Vilsmeier-Haack Reaction of N-Benzyl-1,2,3,4-tetrahydrocarbazole (1) Using Various Formamides (6)

Run	Formamide (6)	Reaction temperature	Products (%)	
			Total yield of (7)[d]	Total yield of (2), (3), and (4) (Isolated yield or ratio)
1	$R^1=R^2=CH_3$[a] (6a)	0°C	0	96.9 (96.9, 0, 0)
2	$R^1=R^2=-(CH_2)_4-$ (6b)	0°C	0	81.0 (81.0, 0, 0)
3	$R^1=R^2=C_2H_5$ (6c)	0°C	0	56.9 (56.9, 0, 0)
4	$R^1=R^2=i\text{-}C_3H_7$ (6d)	0°C	0	0
5	$R^1=CH_3, R^2=C_6H_5$ (6e)	r.t.[c]	78.6	4.2 (4.2, 0, 0)
6	(6a)[a]	120°C	0	63.2 (trace, 37.5, 25.7)
7	(6b)	120°C	0	61.5 (4.6, 36.5, 20.4)
8	(6c)[b]	120°C	14.6	56.6 (24.7, 25.9, 6.0)
9	(6d)	120°C	76.8	0
10	(6e)	120°C	83.4	0

a)Result taken from the previous paper.[2]

b)The Vilsmeier-Haack reaction of N-methyl-THC with 6c was reported[5] to give a 7-formyl derivative as the sole product, but the inaccuracy of this result was pointed out.[6] The present result includes it.

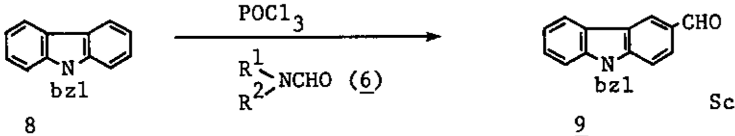
c)The reaction could not be carried out at 0°C, because 6e is a solid in the vicinity of 0°C.

d)The isolated yields of the 5-formyl (7a, oil), the 6-formyl (7b, m.p. 101.5-104°C), and the 7-formyl (7c, m.p. 99-101°C) compounds were 5.7, 20.8, and 56.9%, respectively, in the reaction with 6e at 120°C (run 10).
The ratio in other cases (runs 5, 8, and 9) was similar to the above by measurement with high performance liquid chromatography.

Various electrophilic substitutions are known to occur[4] usually at the 1-position in N-alkyl-THC or at the corresponding position in 1,2,3-trisubstituted indoles. The present result clarifies that these substitutions would generally be caused by an initial *ipso* attack at the 4a-position (or the 3-position of 1,2,3-trialkylindoles) and that the bulky reactive electrophiles attack the benzene moiety instead of the *ipso* 4a-position.

It is synthetically valuable that the Vilsmeier-Haack reaction of 1 with 6e gave mainly the 7-formyl derivative (7c), because we can now expect that appropriate electrophiles toward 1,2,3-trialkylindoles would afford 6-substituted indoles.

Finally, the Vilsmeier-Haack reaction of N-benzylcarbazole (8) with various formamides (6a-e) was carried out to further confirm the prominent reactivity of the reagent from 6e (Scheme 2). The reaction of 8 with $POCl_3$/6e for 1 h gave the 3-formyl derivative (9) in 85.9% at room temperature and in 85.3% yield at 120°C, whereas the reactions with $POCl_3$/6a-d only recovered the starting material (8) at room temperature and gave 9 in poor yields (25.3-32.3%) even at 120°C.



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Scheme 2

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Received, 14th June, 1988