CONVENIENT PHASE TRANSFER N-ARYLATION OF 1,3-DIHYDRO-1,5-BENZODIAZEPIN-2-ONES

El Mokhtar Essassi, Moussa Salem, and Rachid Zniber
Laboratory of Heterocyclic Organic Chemistry, Faculty of Sciences, Rabat, Morocco

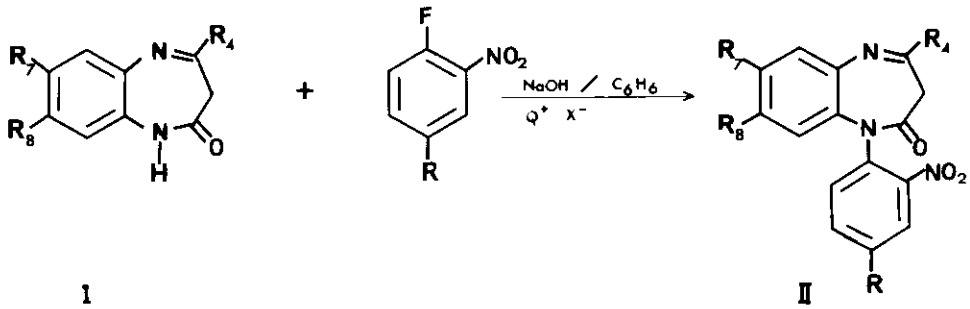
Philippe Viallefont
Laboratory of Heterocyclic Organic Chemistry, U.S.T.L., 34060 Montpellier, France

Roger Gallo
I.P.S.O.I., Fac. Sciences and Techn. St Jérome, 13013 Marseille, France

Abstract - The application of phase transfer catalysis to the N-arylation of heterocyclic molecules is described ; N-arylbenzodiazepines are prepared according to this method. The phase transfer technique is compared to conventional procedures. The dynamic stereochemistry of the ring is evidenced by the change in ^{1}Hnmr spectra line.

Benzodiazepines show marked anxyolytic activity without the sedative effects of barbiturates, or the side effects of the major tranquillizers[1]. Diazepam (valium) chlordiazepoxyde (librium) and clobazam (urbanyl) are among the best known but several benzodiazepine derivatives have been prepared and tested for improved activity. In the course of our recent research on 1,5-benzodiazepines[2,5] we met difficulties in the preparation of N-aryl derivatives when using conventional methods. Therefore we wish to report easy and high yield phase transfer arylation of 1,3-dihydro-1,5-benzodiazepin-2-ones ; this is, to the best of our knowledge, the first application of liquid-liquid phase tranfer catalysis to the N-arylation of heterocyclic compounds[22].

When Ib is reacted with 1-chloro-2,4-dinitrobenzene in the presence of copper and potassium acetate in order to prepare a N-substituted 2,4-dinitrophenyl derivative of Ib, according to the reaction procedure described by Bauer et al.[6], only one coumpound is obtained : 1-(1-phenyl-vinyl)-2-benzimidazolone, which occurs from a 1,3-sigmatropic reaction of the seven membered ring[7]. Even when 1-fluoro-2,4-dinitrobenzene (FDNB) is used under such conditions with the heterocycles Ia-d, N-aryl derivatives IIa-d are obtained with only 10-15% yield. When o-fluoro-nitrobenzene (OFNB) is the arylating reagent no N-aryl compound is obtained. On the other hand the recent literature gives several examples of easy phase transfer catalysed N-alkylation of azaheterocycles e.g. aziridine[8], pyrrole[9,10], indole[11-13], imidazole[14,15], benzimidazole[16], pyrazole[17,18], pyridazinone[19], adenine[20,21], and other pharmaceutical intermediates[22], so far no study of N-arylation of azaheterocycles has been reported. We have carried out these experiments under the following phase transfer conditions : aqueous NaOH (50/50 by weight), benzene, ambient temperature, reaction time ranging from 4 to 12 h and 10% molar quantity of quaternary ammonium catalyst.



I

a_ $R_7 = R_8 = H$; $R_4 = CH_3$; $R = NO_2$

b_ $R_7 = R_8 = H$; $R_4 = C_6H_5$; $R = NO_2$

c_ $R_7 = R_8 = R_4 = CH_3$, $R = NO_2$

d_ $R_7 = R_8 = CH_3$; $R_4 = C_6H_5$; $R = NO_2$, H

II

a_ $R_7 = R_8 = H$, $R_4 = CH_3$; $R = NO_2$

b_ $R_7 = R_8 = H$; $R_4 = C_6H_5$; $R = NO_2$

c_ $R_7 = R_8 = R_4 = CH_3$; $R = NO_2$

d_ $R_7 = R_8 = CH_3$; $R_4 = C_6H_5$; $R = NO_2$, H

The results reported in Table I show that with FDNB the yields are good (65-82%) ; and that they are very little dependent on the substitution of bicyclic compounds ; only when tetrabutyl ammonium iodide is used as catalyst a small yield (40%) is observed. This is consist with the so-called "poisoning" effect of quaternary ammonium iodides which is due in fact to the high solubility of the iodide anion in the organic phase and to a subsequent lack of transfer to the reactive ion-pair from the aqueous to the organic phase[23]. On the other hand the yield of reaction is much dependent on the substitution of the benzene ring and only a 15% yield is obtained with OFNB (o-fluoronitrobenzene). This behavior is typical of the need of activating groups in nucleophilic substitutions at aromatic molecules reactions even under phase transfer conditions : it was already observed during the reaction of phenols with chloropyridines[24].

Table I : **Yields of phase transfer N-arylation of benzodiazepinones** I

Reagent	Compound	Arylating agent[a]	Catalyst (Q^+X^-)[b]	Yield %
Ia	IIa	FDNB	TEBA	80
Ia	IIa	FDNB	$TEBAHSO_4$	70
Ia	IIa	FDNB	TEBAB	65
Ia	IIa	FDNB	TEBAI	40
Ib	IIb	FDNB	CTEAB	82
Ic	IIc	FDNB	CTEAB	78
Id	IId	FDNB	CTEAB	82
Id	IId'	OFNB	CTEAB	15

a : FDNB : fluoronitrobenzene, OFNB : o-fluoronitrobenzene ; b : TEBA : triethylbenzylammonium chloride ; $TBAHSO_4$: tetrabutylammonium hydrogenosulfate. TEBAI : tetrabutylammonium iodide ; CTEAB : cetyltriethylammoniumbromide.

The structure of compounds IIa-d described in Table II are in agreement with analytical and spectral data (ir, ms, nmr). The mass spectra show the main fragmentation pattern of benzodiazepinones : formation of a ketene from the molecular ion[25]. The ^{1}Hnmr spectra deserve a special comment : the methylene of the diazepinone ring appears as a AB quartet, at δ = 3,3-3.7 ppm, wich coalesces at higher temperature to a singlet. This can be attributed to an equilibrium of a diazepine ring between two pseudo-boat conformations[26,28]. This dynamic nmr behavior is further studied.

Table II : **Physical and nmr data of compounds IIa-d**

Compound	*Formula*	*MP°C*[a]	^{1}*Hnmr data*[b]
IIa	$C_{16}H_{12}N_4O_5$	130	2.4(s,3H) ; 3.4(q,2H) ; 7.7(m,7H)
IIb	$C_{21}H_{14}N_4O_5$	170	3.7(q,2H) ; 7.7(m,12H)
IIc	$C_{18}H_{16}N_4O_5$	175	2.1(s,3H) ; 2.3(s,3H) ; 2.4(s,3H) ; 3.3(q,2H);7.6(m,5H)
IIc	$C_{23}H_{18}N_4O_5$	214	2.1(s,3H) ; 2.3(s,3H) ; 3.7(q,2H) ; 7.6(m,10H)
IId'	$C_{23}H_{19}N_4O_5$	123	2.1(s,3H) ; 2.3(s,3H) ; 3.5(q,2H) ; 7.5(m,11H)

a : recrystallized from benzene ; b : recorded with a Perkin Elmer R 12 B (60 Mhz) of Fac. Sci. Rabat ;in $CDCl_3$ 10%, with TMS internal standard ; given in ppm (usual abbreviations).

In conclusion the phase tranfer N-arylation described in this paper is a convenient method which is not limited to benzodiazepinones but could be extented to other azaheterocycles.

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