NUCLEOPHILIC ADDITION OF CARBAZOLES TO VINYL ESTERS

Yu. P. Shekhirev, V. P. Lopatinskii,
V. M. Sutyagin, and S. A. Tuzovskaya

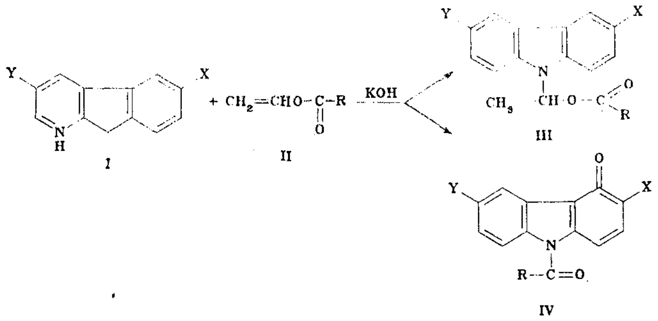
UDC 547.759.32

It has been shown that 3-X-6-Y-carbazoles react in the presence of basic catalysts with vinyl esters simultaneously in two directions to form 3-X-6-Y-N-(α-acyloxyethyl)carbazoles and the corresponding N-acylcarbazoles. The decisive influence of the temperature on the direction of the reaction has been revealed. A mechanism of the process, which is consistent with the kinetic data, has been proposed. A method for the synthesis of the addition products with high yields has been developed.

The addition of vinyl esters to compound containing an NH group followed by pyrolysis of the adducts formed is of interest as one of the methods for obtaining N-vinyl derivatives However, this reaction has been described only for vinyl acetate in several examples.

It was pointed out in [1] that carbazole does not react with vinyl acetate under fairly severe conditions. It is known that the addition of carbazole to acetylene [2], as well as to olefin oxides [3], are conducted in the presence of basic catalysts. The performance of the latter reaction in acetone significantly facilitates it and results in a quantitative yield of the addition product [4].

We undertook an attempt to add carbazole to vinyl acetate in acetone with potassium hydroxide as a catalyst. It was found that under these conditions 3-X-6-Y-carbazoles (I) readily react with vinyl esters (II) with the simultaneous formation of the corresponding adducts: 3-X-6-Y-N-(α-acyloxyethyl)carbazoles (III) and 3-X-6-Y-N-acylcarbazoles (IV):



The reaction of vinyl acetate with carbazole yielded adduct IIIa, which is an isomer of the known [5] N-(β-acetoxyethyl)carbazole. Its chemical properties differ strongly from those of the latter. For example, when heated with water, it is quantitatively hydrolyzed to carbazole, acetaldehyde, and acetic acid, while its β isomer is hydrolyzed only under the action of aqueous solutions of strong bases to N-(β-hydroxyethyl)carbazole. Appreciable decombination of the adducts of type III (except IIIc) also occurs during storage in air.

In order to study the influence of various factors on this reaction we developed a method for the quantitative determination of adducts of types III and IV present together which was based on their different stabilities with respect to hydrolysis. Hydrolysis of the reaction products by water after the complete removal of the ester of type II by washing (test with potassium permanganate) makes it possible to determine the content of the adduct of type III, and hydrolysis by a 0.1 N solution of potassium hydroxide in 5% aqueous methanol [6] makes it possible to determine the sum of the adduct of type III and the acylcarbazole of type IV.

S. M. Kirov Tomsk Polytechnic Institute. Tomsk 634004. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1504-1509, November, 1983. Original article submitted July 14, 1982; revision submitted April 19, 1983.

0009-3122/83/1911-1192$07.50

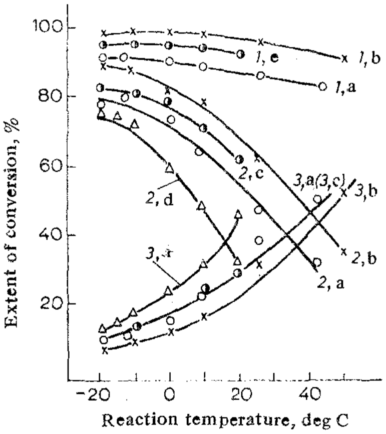


Fig. 1. Influence of the temperature of the reaction of 3-X-carbazoles of type I with esters of type II: 1) total extent of conversion of carbazole I; 2) extent of conversion of carbazole I into adduct III; 3) extent of conversion of carbazole I into acylcarbazole IV; a, b, d) R = CH_3, X = H, Cl, CH_3, respectively; c) R = C_6H_5, X = H; b) according to data in [11]; d) according to data in [14].

As is seen from Fig. 1, the yield of acylcarbazole IV increased with increasing temperature. Therefore, in order to obtain high yields of the adducts it is necessary to maintain a temperature from −10 to −20°C. It is noteworthy that the total extent of conversion of the carbazole varies only slightly in the temperature range from −20 to +50°C, although it has a tendency to decrease with increasing temperature due to secondary processes.

Alkali metal hydroxides, 40-50% aqueous solutions of these bases, and the potassium salts of I served as catalysts from the process under discussion. The application of sodium amide, lithium hydride, calcium hydride, metallic sodium and alkali metal alkoxides does not give any special advantages with respect to the selectivity of the process. However, phase-transfer catalysis of the reaction by tetrabutylammonium bromide results in the predominant formation of the acylcarbazole in the temperature range from +45 to −25°C, i.e., it makes the process selective with respect to the acylation reaction [7]. Variation of the concentration of the catalyst has little effect on the general course of the process, and for preparative purposes it is usually equal to 5-10% of the mass of the original carbazole of type I. In the case of more acidic carbazoles [8], the concentration of the bases may be lower.

During the study of the reaction of the carbazoles with other esters of type II, it was established that the nature of the acidic residue in them has a significant influence not only on the rate, but also on the direction of the process. Elongation of the alkyl radical (R = C_5H_{11}), as well as its replacement by a phenyl radical, have little effect on the course of the process. The introduction of chlorine into an acyl residue, as well as the replacement of an acetyl residue by a formyl residue not only sharply lowers the rate of the process, but also causes the reaction to proceed practically only in the acylation direction with the formation of the corresponding acylcarbazoles.

As a result of the investigations carried out, a general method for the synthesis of adducts of type III with high yields, and the possibility of the synthesis of various acylcarbazoles of type IV with the aid of esters of type II was demonstrated. It is noteworthy that the acylcarbazoles of type IV are obtained by this method under mild conditions with a high degree of purity. This method of synthesis is conveniently employed when the corresponding anhydrides or acid halides are unknown or relatively inaccessible. The results which we obtained are given in Table 1.

On the basis of the kinetic data in [17] the mechanism of the reaction under consideration includes the fast equilibrium ionization of the carbazole (I) under the action of the base introduced (1) and a rate-limiting step (2), i.e., the attack of the carbazole anion on the ester molecule at the carbonyl carbon atom and the α-carbon atom of the vinyl group to form an intermediate transition complex (A), which then isomerizes to the two intermediate anions A_1 and A_2 (3), from which an adduct of type III and an acylcarbazole of type IV form.

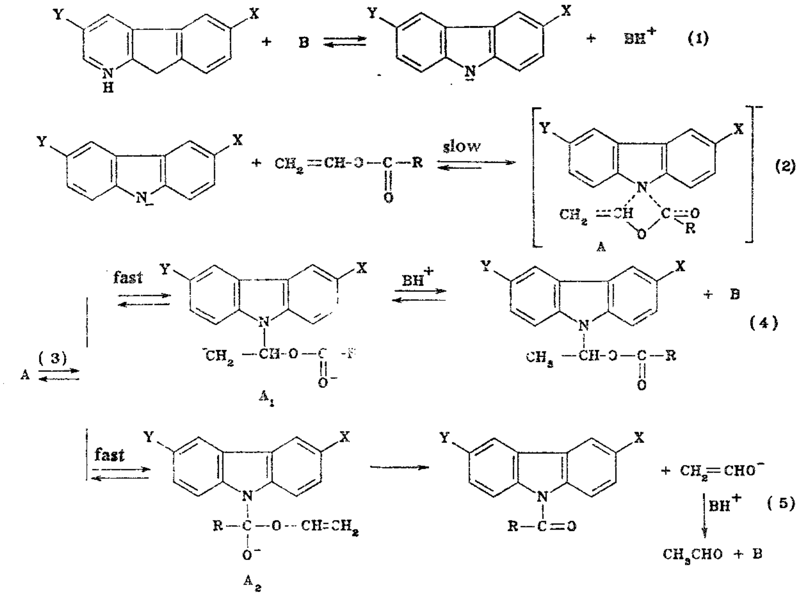
The proposed mechanism is in good agreement with the experimental data. We showed that the reaction can be carried out in ketones, dimethylformamide, dimethyl sulfoxide, and other aprotic dipolar solvents, which promote the ionization of the carbazole as an acid. The reaction does not occur in aprotic nonpolar solvents (benzene, dioxane), which do not promote the ionization of the carbazole.

TABLE 1. Synthesis of 3-X-6-Y-N-(α-Acyloxyethyl)carbazoles (III) and 3-X-6-Y-N-Acylcarbazoles (IV)

Compound	X	Y	R	Reaction temperature, deg C	mp, deg C	Literature	Found, %			Empirical formula	Calculated, %			Yield, %
							C	H	N		C	H	N	
IIIa	H	H	CH_3	from −20 to −10	90—92	[9]	75,8	5,9	5,6	$C_{16}H_{15}NO_2$	75,8	5,9	5,5	71—84
IVa	H	H	CH_3	30	74—75	[10]	80,4	5,2	6,7	$C_{14}H_{11}NO$	80,4	5,3	6,7	45
IIIb	Cl	H	CH_3	from −20 to −10	90—91	[11]	66,6	4,6	4,8	$C_{16}H_{14}NO_2Cl$	66,7	4,9	4,9	67—71
IVb	Cl	H	CH_3	30	124—125	[12]	69,3	4,2	5,6	$C_{14}H_{10}NOCl$	68,9	4,1	5,8	38
IIIc	NO_2	H	CH_3	from −20 to −10	182—183	—	64,1	4,7	9,3	$C_{16}H_{14}N_2O_4$	64,4	4,7	9,4	64—71
IVc	NO_2	H	CH_3	30	235—237	[13]	64,1	4,7	9,3	$C_{16}H_{14}N_2O_4$	64,4	4,7	9,4	40
IIId	CH_3	H	CH_3	from −20 to −10	84—85	[14]	—	—	—	$C_{17}H_{17}NO_2$	76,4	6,4	5,2	60—68
IVd	CH_3	H	CH_3	50	74—75	—	—	—	6,4	$C_{15}H_{13}NO$	80,7	5,8	6,3	48
IIIe	H	H	C_5H_{11}	−20	46	—	77,5	7,4	4,4	$C_{20}H_{23}NO_2$	77,8	7,4	4,5	72—73
IVe	H	H	C_5H_{11}	30	67—68	—	81,4	7,1	5,1	$C_{18}H_{19}NO$	81,5	7,2	5,3	15—19
IIIf	H	H	C_6H_5	from −20 to −10	103—104	—	79,9	5,3	4,5	$C_{21}H_{17}NO_2$	80	5,4	4,4	71—73
IVf	H	H	C_6H_5	30	98	—	—	—	5,3	$C_{19}H_{13}NO$	84,1	4,8	5,2	31—37
IVh	H	H	CH_2C	30	98—100	[16]	—	—	—	$C_{14}H_{10}NOCl$	69	4,1	5,8	Traces
IIIi	Cl	Cl	CH_3	−20	162—164	—	—	—	4,5	$C_{16}H_{13}NO_2Cl_2$	59,8	4,0	4,4	85—90
IVi	Cl	Cl	CH_3	43	184—186	[12]	—	—	—	$C_{16}H_{13}NOCl_2$	63	4,3	4,6	93—98
IVg	H	H	H	30	98—100	—	79,9	4,6	7,1	$C_{13}H_9NO$	80,0	4,6	7,2	31—37

The introduction of electron-acceptor substituents into the molecule of the carbazole of type I lowers the electron density on the atom of the imino group and increases its strength as an acid [8]. The investigation of the kinetics of the reaction of the carbazoles of type I with vinyl acetate showed that their reactivity is described by a Hammett equation with the form $\log K/K_0 = -4.2\Sigma\sigma$. The relatively large negative value of ρ is an indication of the high sensitivity of the reaction to the electronic influence of the substituents. The thermodynamic activation parameters of the reaction resulting in the formation of the adduct of type III are: $E = 8.3 \pm 0.9$, $\Delta H = 7.1 \pm 0.4$ kJ/mole, and $\Delta S = -258.2 \pm 12.4$ J/mole·deg. The values for the formation of the 9-acylcarbazoles are: $E = 36.6 \pm 1.9$, $\Delta H = 29.3 \pm 1.6$ kJ/mole, $\Delta S = -239.0 \pm 11.2$ J/mole·deg. The quantitative interpretation of the entropy of activation of the reactions considered suggests that there are orientational and steric requirements for the formation of the transition state, which are characteristic of bimolecular processes [18]. The significant difference between the activation energies accounts well for the influence of the temperature on the yields of the two possible reaction products.

Scheme of the mechanism of the reaction of carbazoles with vinyl acetate under the conditions of base catalysis



The electron density in the molecule of vinyl acetate [19] is distributed in such a manner (Fig. 2) that it has two electrophilic centers, viz., the carbonyl carbon atom and the α-carbon atom of the vinyl group, to which the attack of the anion of the carbazole of type I is directed to form the intermediate transition complex A. In the case under consideration here, the distribution of the π components of the atomic charges (D), which, as is seen from Fig. 2, is different for vinyl formate and vinyl acetate, rather than the distribution of the total atomic charges (C), is of greatest importance. According to this distribution, the α-carbon atom in vinyl formate has a negative charge, as a result of which the attack of the anion of a carbazole of type I on it is impossible, and an addition reaction does not take place. The attack on the carbonyl carbon atom, as previously, can be realized, and the formylcarbazole forms. A similar phenomenon is apparently observed in the case of vinyl monochloroacetate. In the case of other esters of type II ($R = C_5H_{11}$ or C_6H_5), the distribution of the electron density is similar to that in vinyl acetate, and the reaction can take place in the two directions. All other conditions being equal (Fig. 1), a greater yield of adduct IIIf is always observed in the case of vinyl benzoate than in the case of vinyl acetate. This is possible due to the fact that the α-carbon atom in vinyl benzoate has a greater positive charge than in vinyl acetate due to the conjugation of the phenyl residue to the remainder of the molecule.

EXPERIMENTAL

Pure-grade carbazole was recrystallized from acetone to mp 243-244°C. Its derivatives, which were synthesized according to the methods in [12, 20-22], had mp 192-193°C ($X = Cl$, $Y = H$), 205-212°C ($X = NO_2$, $Y = H$), 202-203°C ($X = CH_3$, $Y = H$), 202-203°C ($X = Y = Cl$).

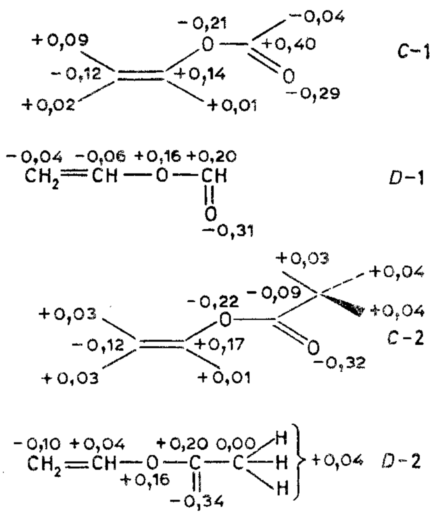


Fig. 2. Distribution of the total atomic charges (C) and their π components (D) in the molecules of vinyl formate (1) and vinyl acetate (2). Calculation by the CNDO/2 method [19].

The esters of type II were obtained via vinyl interchange [23] of vinyl acetate with the corresponding acids.

3-X-6-Y N-(α-Acyloxyethyl)carbazoles (III). A mixture of the carbazole of type I and the ester of type II in a 1:1.5 ratio (mole/mole) in acetone (5 ml per gram of the carbazole) at a temperature from −10 to −20°C is given an addition of finely ground KOH (5-10% of the mass of the carbazole) and held for 30 min. The reaction mass is filtered, the acetone is distilled off, and the remaining oil is dissolved in hexane or other hydrocarbons (5-10 ml per gram of the carbazole) with heating. The mixture is cooled, and the adduct of type III is filtered out and recrystallized from the same solvent. The compound of type III must be stored in a sealed ampul or under a hydrocarbon layer.

In the synthesis of IIIc, the reaction products remain in the precipitate at the end. They are filtered out, washed with water, and dissolved with heating in acetone or benzene (40 ml per gram of the carbazole). The mixture is cooled to room temperature and acylcarbazole IVc is filtered out. Half of the solvent is distilled off from the filtrate, the filtrate is cooled, and the stable adduct IIIc is filtered out and crystallized from the same solvents.

3-X-6-Y-N-Acylcarbazoles (IV). The reaction is carried out in a similar manner at 30-50°C. The reaction mass is poured into water, the precipitate is filtered out and treated with ethanol (3 ml per gram of the carbazole) at the boiling point, and the undissolved carbazole of type I is filtered out. The acylcarbazoles (IV) crystallize from the filtrate upon cooling. The separation of compounds IIIc and IVc is carried out by fractional crystallization, as described above.

LITERATURE CITED

1. I. Furukawa, A. Onishi, and T. Tsuruta, J. Chem. Soc. Jpn., Ind. Chem. Sec., 60, 179 (1957).
2. A. D. Petrov (ed.), The Chemistry of Acetylene [in Russian], IL, Moscow (1954).
3. G. S. Kolesnikov, Synthesis of Vinyl Derivatives of Aromatic and Heterocyclic Compounds [in Russian], Izd. Akad. Nauk SSSR, Moscow (1960), p. 304.
4. V. P. Lopatinskii, E. E. Sirotkina, and I. P. Zherebtsov, USSR Patent No. 159,533; Byull. Izobret., No. 1, 16 (1964).
5. R. Flowers, H. Miller, and L. Flowers, J. Am. Chem. Soc., 70, 3019 (1948).
6. V. P. Lopatinskii and Yu. P. Shekhirev, Izv. Tomsk. Politekh. Inst., 163, 32 (1970).
7. V. P. Lopatinskii, S. A. Tuzovskaya, and V. M. Sutyagin, Article deposited in the Cherkassy Branch of the Scientific-Research Institute of Technical and Economic Research of the State Committee of the Council of Ministries of the USSR for Chemistry No. 270-XII-D82; Dep. Ruk., No. 6, 11 (1982).
8. I. P. Zherebtsov and V. P. Lopatinskii, Izv. Tomsk. Politekh. Inst., 163, 12 (1970).
9. V. P. Lopatinskii and Yu. P. Shekhirev, Izv. Tomsk. Politekh. Inst., 136, 162 (1965).
10. V. P. Lopatinskii, E. E. Sirotkina, and M. M. Anosova, Izv. Tomsk. Politekh. Inst., 112, 36 (1963).

11. V. P. Lopatinskii, Yu. P. Shekhirev, V. M. Sutyagin, and E. A. Danilova, Izv. Tomsk. Politekh. Inst., 163, 28 (1970).
12. G. Mazzara and E. Lamberti-Zanardi, Gazz. Chim. Ital., 26, II, 236 (1896).
13. I. M. Heilbron and H. M. Bunbury, Dictionary of Organic Compounds, Eyre and Spottiswoode, London (1947).
14. V. P. Lopatinskii, Yu. P. Shekhirev, V. M. Sutyagin, and V. P. Chernitsina, Izv. Tomsk. Politekh. Inst., 163, 172 (1970).
15. T. Stevens and S. Tucher, J. Chem. Soc., 123, 2140 (1923).
16. R. Donhlom, Acta, Chem. Scand., 6, 309 (1952); Chem. Abstr., 47, 3848 (1953).
17. V. M. Sutyagin, V. P. Lopatinskii, and S. A. Tuzovskaya, in: Aspects of Kinetics and Catalysis [in Russian], Ivanovo (1982), p. 107.
18. H. Becker, Einfuehrung in die Elektronentheorie organisch-chemischer Reaktionen, VEB Beutscher Verlag der Wissenshaften, Berlin (1961).
19. Yu. E. Éizner and B. L. Erusalimskii, Electronic Aspect of Polymerization Reactions [in Russian], Nauka, Leningrad (1976), p. 180.
20. R. K. Éikhman, V. O. Lukashevich, and E. A. Silaeva, Prom. Org. Khim., 6, 93 (1939).
21. T. C. Whitner, J. Am. Chem. Soc., 46, 2326 (1924).
22. W. Borche, A. Witte, and W. Bonte, Ann. Chem., 359, 74 (1908).
23. R. Adelman, J. Org. Chem., 14, 1057 (1949).

SYNTHESIS OF 3-SUBSTITUTED 4-PIPERIDONES

G. V. Grishina, V. M. Potapov,
S. A. Abdulganeeva, and I. A. Ivanova

UDC 547.824'828.07:541.62:543.422

It has been shown that the addition of methyl acrylate and acrylonitrile to the pyrrolidine enamines of 1-methyl-, (1S)-α-phenylethyl-, (1S)-sec-butyl-, 1,2-dimethyl-, and 1,3-dimethyl-4-piperidone results in the formation of 3- or 5-substituted 4-piperidones, depending on the reaction conditions and the structure of the enamine. The formation of a pair of diastereomers of the 3-substituted 4-piperidones in a 1:1 ratio takes place when there is a chiral substituent on the nitrogen atom in the piperidone ring.

In the framework of the study of asymmetric reactions in a series of 4-piperidones, we investigated the possibility of the transmission of the asymmetric effect of a chiral substituent on the nitrogen atom when a new carbon—carbon bond forms. As a model reaction we selected the formation of 3-substituted 4-piperidones by the addition of methyl acrylate and acrylonitrile to enamines of 4-piperidones. Since there is only one report in the literature on the cyanoethylation of the pyrrolidine enamine of 1-methyl-4-piperidone [1], it was necessary to work out the conditions and to establish the stereochemical laws for the addition of methyl acrylate and acrylonitrile to the pyrrolidine enamines of 4-piperidones. The addition of methylacrylate and acrylonitrile to the pyrrolidine enamines and 1-methyl- (IIa), (1S)-α-phenylethyl- (IIb), (1S)-sec-butyl- (IIc), 1,2-dimethyl- (IId), and 1,3-dimethyl-4-piperidone (IIe).

The enamines of type II were obtained by boiling the 4-piperidones (I) with a 0.5-molar excess of pyrrolidine in absolute benzene in an argon atmosphere. It should be noted that all the enamines of type II are unstable and readily decompose on silica gel and during storage. The structure of enamines IIa-c was confirmed by the presence in the PMR spectra of a characteristic triplet of the vinyl proton at 4 ppm and by the presence in the IR spectra of bands of the stretching vibrations of the enamino group at 1660-1670 cm^{-1}. Two enamines, IIdA and IIdB, form from 1,2-dimethyl-4-piperidone, since two signals, viz., a triplet at 4.1 and a doublet at 3.91 ppm, are observed in the PMR spectrum in the region of the vinyl protons, the ratio between their integrated intensities being 1:1. According to the PMR data, only enamine IIe forms from 1,3-dimethyl-4-piperidone. This was established on the basis of

---

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1510-1514, November, 1983. Original article submitted May 17, 1983.

0009-3122/83/1911-1197$07.50