MOLECULAR DESIGN OF HETEROCYCLES. 3.* THE "LAST" TWO-COMPONENT TYPE OF SYNTHESIS OF PYRIDINE RING BY INSERTION OF A β-CARBON ATOM: REVIEW OF APPROACHES AND EXPERIMENTAL REALIZATION IN A NEW SYNTHESIS OF QUINOLINES (REVIEW)

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This review, which includes an experimental section, deals with two-component syntheses of six-membered heterocycles by the interaction of acyclic 1,5-bielectrophiles (or their heterocyclic analogs) and binucleophilic nitromethane. A previously unknown type of synthesis of the pyridine skeleton has been accomplished experimentally in the example of obtaining 3-nitro-4-quinolinone from the formamidine of anthranilic acid and nitromethane.

A great variety of structural types of syntheses of six-membered heteroatomic systems is the subject of a detailed review [2], in which a convenient classification is proposed for two-component syntheses of the 5+1 type, this classification indicating the location of the inserted atom relative to the heteroatom of the final ring. In particular, α-insertion and γ-insertion of the carbon atom (or heteroatom) are distinguished, and also the insertion of the heteroatom itself. As regards syntheses based on insertion of atoms into the β-position, the authors of the review [2] mention only one example of the use of an electrophilic nitrogen atom in forming a 1,2,4-triazine ring — a synthesis, let us note, that can be equally interpreted as γ-insertion.

A similar gap in the information is noted in reviews on syntheses of heterocycles containing the simplest azine nucleus — pyridine. For example, in the review [3], along with a detailed analysis of syntheses of the pyridine ring by α- or γ-insertion, the β-insertion method simply does not appear in the index; also, this synthesis route is not considered in other reviews (see bibliography in [1]).

The present review is aimed at filling in this gap in the literature, by two approaches. In the first place, we will review the published information on syntheses of six-membered heteroaromatic rings (primarily the pyridine ring) in which such a type of synthesis (or something analogous to β-insertion) *was* realized, or even *could be* realized. In the second place, we will depart slightly from the actual review to present information on our experimental realization of the concept of β-insertion in the example of a previously unknown synthesis of the pyridine fragment of the quinoline nucleus.

In an earlier communication [1] we formulated a number of empirical "magic" rules for the synthesis of compounds of the class of six-membered heterocycles. These rules, for example, make it possible to predict the optimal combination of electrophilic and nucleophilic centers in reagents if there is an indication of the specific positions in which the skeletal bonds of the ring must be created. For the special case of β-insertion of a carbon atom (relative to the pyridine heteroatom), the proposed heteroalternation rule [1] necessarily requires *binucleophilicity* of the β-atom that is inserted and *bielectrophilicity* of the five-membered chain.

Let us note that an example of a synthesis with such a distribution of functions in the reagents is well known in the benzopyran series [4]. This is the synthesis of chromenes on the basis of a 1,1-binucleophilic phosphonium ylide and a 1,5-bielectrophilic chain, reaction (1):

*For Communication 2, see [1].

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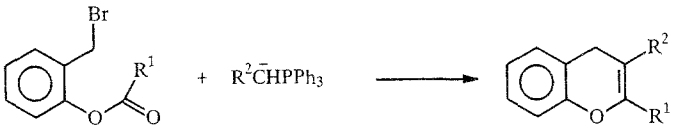


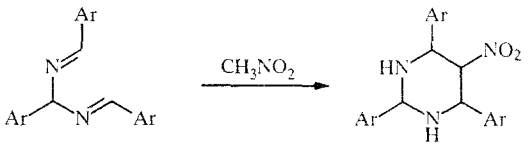
(1)

R^1 = Alk, Ar; R^2 = Ph, Ac, CO_2Me

However, this example apparently exhausts the known utilization of ylide reagents in such syntheses. Among the other known carbon 1,1-binucleophiles (for example, the dimethylsulfoxide anion, α-methyl-substituted azines, their cations, etc.), which are potentially free to exchange two CH-acidic protons with other appropriate electrophiles, we have not been able to find any adequate examples. Nitromethane is the only widely used carbon-containing 1,1-binucleophile in syntheses of heterocycles.

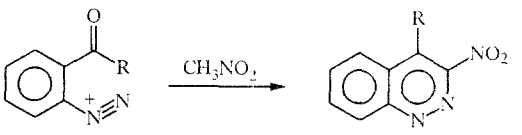
Binucleophilic nitromethane, is capable, in principle, of closing any bielectrophilic chain, for example an odd-membered carbocyclic chain, as in the synthesis of 2-nitronaphthalene from homophthalic dialdehyde [5] (compare the syntheses of a benzene ring using glutaconic dialdehyde and CH-acids [6, 7]). Analogously, in the presence of an appropriate 1,4-bielectrophile, it is easy to close a five-membered carbocyclic ring [5, 8] or the heterocyclic pyrrole ring [9]. (In the latter case, the pyrrole fragment has been annelated successfully to the skeleton of quinoline or isoquinoline [10].)

However, in the field of synthesis of azines by reactions of nitromethane with acyclic 1,5-bielectrophiles, there is an unexplained gap in the literature. In such reactions, with β-insertion, we would expect the formation of six-membered β-nitrohetarenes. Let us note in this connection that two recent reviews devoted to syntheses of the class of β-nitroazines as a whole [11], and to the synthesis of β-nitropyridines [12], leave this problem virtually untouched. We know of only two examples of such syntheses: the recently discovered [13] path of assembly of a saturated pyrimidine skeleton that starts with a Schiff base, reaction (2)



(2)

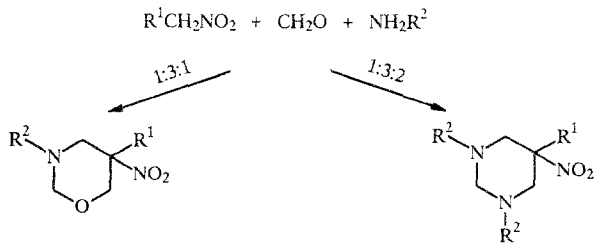
and an earlier example [14] of the synthesis of cinnolines by the Baumgarten method from aryldiazonium salts and nitromethane, reaction (3)



(3)

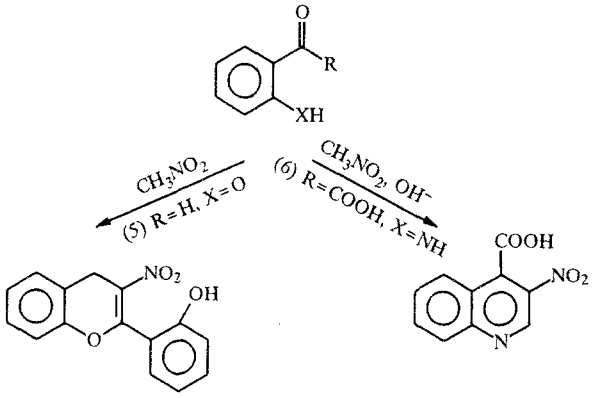
Two other examples of condensations of 1,5-bielectrophiles with nitromethane are known (the synthesis of γ-nitrothiapyran [15] and the closure of the skeleton of cyclo[3,2,2]azine by γ-insertion to the heteroatom [16]), which, however, do not fall under the category of β-insertion that we are considering here.

There are many multicomponent syntheses in which nitromethane, in an unknown stage, enters into the β-position relative to the heteroatom of a six-membered ring. We will limit ourselves to a characteristic example [17, 18] in which the type of the heterocycle that is obtained is determined by the stoichiometry of the reagents, reaction (4):

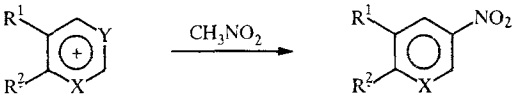


(4)

Bordering on this same class are three-component syntheses of the 4+1+1 type, including autocondensation of one of the reagents, again with β-insertion of nitromethane in one of the stages. In one of these syntheses, reaction (5), upon formation of the chromene, the original salicylaldehyde is self-condensed [19]; in the other synthesis, reaction (6), it appears that the nitromethane is subject to self-condensation, with the intermediate formation of metazonic acid [20]:*



The vacuum that exists in the field of syntheses of β-nitroazines by cyclization from acyclic 1,5-bielectrophiles is, in effect, compensated by examples that are known (and cited in the reviews [2, 3, 5, 7, 11, 12]) of the recyclization of azinium cations under the influence of nitromethane, which is characterized in general form by reactions (7), (8), and (10):



R^1, R^2	Substitutents			-CH=CH—CH=CH-	
X	N	N	CH	N	CH
Y	O	NR	O	NR	NR
Reaction	(7)	(8)	(9)	(10)	(11)

Formally, such heteroalternant [1] cations containing heteroatoms in the *meta* position relative to each other will really act as masked forms of 1,5-bielectrophiles, the closing heteroatom of which is replaced by a nitromethine group in the course of the reaction. such reactions are completely analogous to the transformations of simpler 1,5-bielectrophilic rings (with one heteroatom), which, under the influence of nitromethane, are converted to carbocyclic systems — for example, recyclizations of pyryllium salts to nitrobenzenes [21] or of N-methylquinolinium to 2-nitronaphthalene [22], reactions (9) and (11). This analogy, however, is not complete: As noted above, not only recyclizations but also "simple" cyclizations lead to carbocycles, in contrast to the situation for heterocycles.

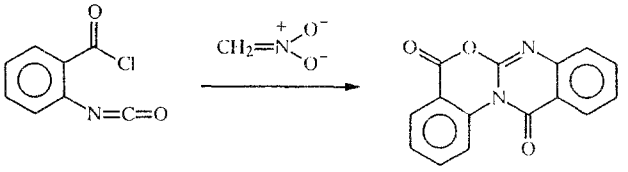
Unfortunately, the circle of such transformations cannot be extended to noncationoid heterocycles (with the same structure of the masked 1,5-bielectrophiles), for example to oxo or dioxo derivatives of 1,3-oxazines. Recyclization under the influence of nitromethane in such systems is complicated by the fact that cleavage of the ring in many cases is not accompanied by subsequent closure of the new ring. This is precisely the way that 4H-1,3-benzoxazinone behaves [23]. Isatoic anhydride [23], its pyridine aza analog [24], or 1,3-oxazine-2,4-dione [25], under the influence of nitromethane, opens its ring with the loss of a molecule of CO_2, which contained a potential center for closure of a new ring.

In the above discussion we drew two parallels — on the one hand between the synthesis of carbocycles and heterocycles, and on the other hand between cyclizations and recyclizations. A third constructive type of analogy is possible, specifically the analogy between the 1,1-binucleophilic properties of nitromethane and ammonia [1]. In particular, most of the reactions considered above will proceed successfully when nitromethane is replaced by ammonia. Let us note in this connection

*The original compound in reaction (6) was isatin, which, in alkaline solution, is split quantitatively to form isotoic acid.

that recyclizations under the influence of ammonia are well known for both pyryllium and 1,3-oxazinium salts, with replacement of the nitrogen atom by oxygen [26], as well as recyclizations of acyclic five-membered chains that lead to the same cyclic products — pyridines or pyrimidines [2].* Benzannelated systems behave analogously. In other words, for ammonia as a 1,1-binucleophile, experimental confirmation has been obtained for the *equivalence of cyclization and recyclization* when using 1,5-bielectrophiles (either explicit or latent in the ring). For the binucleophilic nitromethane, only recyclizations are represented.

In this connection, the absence of any reports of reactions of β-insertion type reactions in the interaction of nitromethane with appropriate acyclic 1,5-bielectrophiles (with the formation of β-nitropyridines or β-nitroquinolines) should be considered as some sort of a "historical misunderstanding." The decisive factor in why these syntheses have not yet been discovered should be sought in the ambidentate nature of nitromethane (in contrast to ammonia). In fact, reactions with alkylating or acylating agents in the rarest cases [17, 18, 23, 27] proceed at the carbon atom, since attack of the electrophile at the oxygen atom is kinetically preferred [28]. One of the rare examples of electrophilic attack at the carbon atom is the reaction of nitromethane [29] with arylisocyanates. (Nitroethane is attacked at the oxygen atom [30].) Meanwhile, even when a suitable 1,5-bielectrophilic substrate was available, Indian investigators reported in [31] that they were not able to "force" reaction (10) to proceed in the required direction corresponding to β-insertion:



(10)

As a result of congruent electrophilic attack at the oxygen atom of the nitromethane anion, a different direction of the reaction was realized. Let us note that the methodology of nitromethane conversion (by double deprotonation) with a single-function C-nucleophile, as developed in [27], could lead to success and to the discovery of a new type of quinoline synthesis on the basis of the principle of β-insertion. In the analogous reaction with ammonia, the expected quinazoline ring is formed (O- and S-nucleophiles behave in the same way [32, 33]).

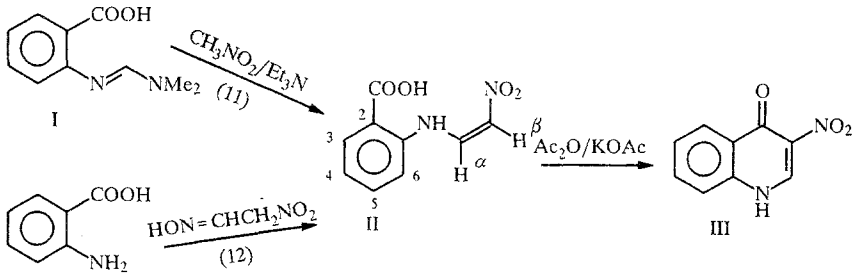
As can be seen, the design of cyclization reactions with the participation of nitromethane, on the basis of a simple analogy with ammonia, encounters objective difficulties. In attempts to detect experimentally the last "allowed" [1] type of synthesis of the pyridine ring (coming under the category of β-insertion), specifically for reactions of nitromethane, we carried out a thorough screening of appropriate substrates. The required bielectrophilic chain must not only match the sequence of centers C—C—C—N—C, but it must also be capable of reacting with nitromethane, specifically forming a new C—C bond. Another serious difficulty was in selecting a specific one-carbon function at the edge of the chain such that its electrophilicity would not be suppressed by the adjacency of the nitrogen atom.

In analyzing the potentially suitable fragments, we turned our attention to the views expressed in a paper by a group of Polish investigators [34], who noted that primary nitroalkanes formed crystalline compounds with diphenylformamidine in much the same manner in which they react with diazonium salts; compare reaction (3). Unfortunately, this work was never published in the open literature. Analysis of reviews and monographs on the chemistry of amidines [35, 36], along with a running search through abstract journals, showed that no preparative reactions are known for obtaining amidines from nitroalkanes. A cation that is a vinylog of amidines ("vinamidinium") reacts in the expected manner, forming a C—C bond with nitromethane [37].

A suitable objective in the search for a new synthesis of the pyridine ring thus proved to be a conjugated system with an amidine function at one of the ends. Of a number of possible amidine substrates, we selected one that is described in the literature, N,N-dimethyl-N′-arylformamidine I, obtained by the Vilsmeier reaction from the readily available anthranilic acid [38]. The principles governing this selection were obvious: In the first place, it is well known that such amidines are readily cyclized under the influence of ammonia to form the corresponding quinazolinones [36]. In the second place, nucleophilic

*This type of synthesis, which was interpreted in [2] as the insertion of a heteroatom, in the case of pyrimi- [no further material in footnote in Russian original — Translator].

displacement of the dimethylamino group in the formamidine fragment by nitromethane through the hypothetical reaction (11) would lead to the formation of the nitroenamine II. Compound II not only has been described previously, but is also capable of being cyclized to the known 3-nitro-4-quinolone III [39]. Thus, compound II could be counter-synthesized from metazonic and anthranilic acids by a known procedure, reaction (12).



In the end, detection of the "elusive" two-component synthesis of the pyridine skeleton in the composition of the quinoline nucleus might be reduced to a combination of an unknown intermolecular reaction followed by a known intramolecular cyclocondensation.

It was found that reaction (11), the conversion of the amidine I to the enamine II under the influence of nitromethane, proceeds with a 62% yield. The structure of compound II was confirmed by counter-synthesis through reaction (12). On the basis of PMR spectrometric data, compound II has the enamine structure (not the previously ascribed imine structure [39]) with a *cis* position of the substituents.

The subsequent cyclization to nitroquinolone III was trivial [40]. The reaction path that is proposed, apart from its novelty, has at least two advantages. In the first place, it is safe, in contrast to the use of the sometimes explosive [40] metazonic acid. In the second place, reaction (12) (and the resulting class of 3-nitroquinolines) has a rather unexpected application [41] in the synthesis of isotope-labeled nicotinic acids (after removal of the nitro group and oxidative cleavage of the benzene ring). Only the carbon atoms brought in by the metazonic acid have thus far been labeled successfully; the metazonic acid was obtained in turn from labeled nitromethane; compare reaction (6). The new synthesis also opens up fresh approaches in this area. Let us note, finally, that Molina [42], who used nitromethane and heterocumulenes for the synthesis of the pyridine ring through the aza-Wittig reaction (principle of α-insertion), would have been extremely close to finding the reaction of β-insertion if the sequence of adding the reagents had been reversed.

EXPERIMENTAL

Procedures given in [39] were used to obtain: metazonic acid (by the interaction of nitromethane with a KOH solution, the product being used without segregation); **2-(2-nitroethylidenamino)benzoic acid (II)** (obtained by reaction of metazonic and anthranilic acids, yield 98%); **3-nitro-4-quinolone (III)** (by heating compound II in acidic anhydride with the addition of potassium acetate, yield 43%).

Hydrochloride of N,N-dimethylformamidinoanthranilic acid (I) was obtained by a procedure given in [38], from anthranilic acid and a mixture of dimethylformamide with thionyl chloride, yield 95%.

Interaction of Hydrochloride of N,N-Dimethylformamidinoanthranilic Acid with Nitromethane and Triethylamine. The hydrochloride of N,N-dimethylformamidinoanthranilic acid (1.14 g, 5 mmoles) was added to a solution containing 5 ml of DMF, 0.4 ml (7.5 mmoles) of nitromethane, and 2.5 ml (17.5 mmoles) of triethylamine. In 10-15 min, the solution took on a bright yellow color. The reaction mixture was left for 12 h at room temperature and then heated for 15 min at 80°C. The solution was poured into 50 ml of water and extracted with ether (3 × 40 ml), and the ether extract was evaporated. The residue was chromatographed in a column (Silperl, ether–petroleum ether, 2:1). The first fraction (after evaporation) contained a small quantity of anthranilic acid. The second fraction (yellow) was collected. After evaporation, recovered 0.64 g (62%) of a yellow substance, mp 196-196°C, identical to 2-(2-nitroethylidenamino)benzoic acid (no melting point depression in a mixed sample; identical chromatographic behavior in mixtures of various eluents). PMR spectrum (400 MHz, DMSO-d_6): 7.24 (1H, m, J = 8.0 Hz, J_{45}= 7.7 Hz, J_{46} = 1.1 Hz, 4-H); 7.63 (1H, m, J_{54} = 7.7 Hz, J_{56} = 7.8 Hz, J_{53} = 1.5 Hz, 5-H); 7.76 (1H, dd, J_{65} = 7.8 Hz, J_{64} = 1.1 Hz, 6-H); 8.04 (1H, dd, J_{34} = 8.0 Hz, 3-H); 6.67 (1H, d, $J\alpha,\beta$= 6.2 Hz, β-H;) 3.06 (1H, dd, $J\beta,\alpha$ = 6.2 Hz, $J\beta,_{NH}$ = 13.5 Hz, α-H); 13.05 (1H, d, J_{NH},β = 13.5 Hz, NH).

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