MODIFIED POLONOVSKI REACTION, A VERSATILE SYNTHETIC TOOL

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Abstract - Recent synthetic applications of the modified Polonovski reaction are reviewed. In particular, the mechanistic consequences of the reaction are discussed.

Designing the synthesis of a complex organic molecule such as several alkaloids often involves the strategist in questions of formidable difficulty. It can be argued that many of the greatest achievements of synthetic organic chemistry have come within the past two decades, and one can only presume that an increasing rate of new syntheses (sensu stricto, see ref. 1) will be achieved in the future. Of vital importance to the development of new efficient and elegant syntheses is the discovery of new selective chemical transformations, the unit processes which the organic chemist uses as "building blocks" in designing and executing a synthetic strategy and plan in detail.

Piperidine unit is an abundant feature of several natural products, as exemplified by corynantheidine 1, (+)-20-epiuleine 2, histrionicotoxin 3, ψ-pelletierine 4 and morphine 5 in Chart 1. Beyond doubt, the achievement of the correct substitution pattern in the piperidine ring has been a vexed problem. The development of the modified Polonovski reaction has provided a versatile approach to various substituted piperidine systems, in offering a general method of constructing a 5,6-dihydropyridinium system 6 which is susceptible to the attack of carbon nucleophiles in a desired conjugated addition manner. In addition to being a useful means of preparing the dihydropyridine equivalent 6, the modified Polonovski reaction is also amenable to generating α-amino-nitriles, synthons of wide applicability in both nucleophilic and electrophilic reactions.

I POLONOVSKI REACTION

I-1 Mechanism

Already in 1927 Max and Michel Polonovski observed that tertiary amines can be demethylated by treating the corresponding N-oxide 7 with acid anhydride. The main products of the reaction were found to be the N-acylated N-demethylamine 8 and formaldehyde (Equation 1).
Chart 1

$R - CH - NH_2 \stackrel{Ac_2O}{\longrightarrow} R - CH - N - CH_3 + Ac - NH_2 + CH_2O$

Equation 1
Only nearly three decades later, in 1954, Wenkert proposed a mechanism for the reaction. This proposition was based on theoretical considerations: to explain the formation of the Polonovski products from compounds with the nitrogen at a bridgehead position, an ylide mechanism was needed so as to avoid violation of the Bredt’s rule (Scheme 1). Huisgen et al. undertook a more careful study on the mechanism of the Polonovski reaction and were able to provide substantial evidence in favor of the mechanism outlined in Scheme 2. They also considered a radical mechanism possibility, as the Polonovski reaction of N,N-dimethyl aryl amine N-oxides had been reported to induce polymerization of styrene. However, this phenomenon was attributed to a side reaction with high temperature coefficient. The intramolecular ylide mechanism of Wenkert was also cast aside, because the reaction was observed to follow a base-catalyzed E2-elimination scheme.

Later, Huisgen and Kolbeck were able to show that, at least in the case of quinuclidine N-oxide, the Bredt’s rule was not violated. The only product isolated (in nearly quantitative yield) was the remarkably stable N-acloxyquinuclidinium salt. The benzoylquinuclidinium compound resisted further reaction to give the Polonovski reaction products.
As previously mentioned, on the basis of the observation that the rearrangement of \( N,N \)-dimethyl-
aniline \( N \)-oxide in boiling benzene is effective in causing styrene polymerization,\(^8\) a radical
mechanism for the Polonovski reaction was advanced. Thus, the ylide \( 12 \) was supposed to be cleaved
homolytically into the radical pair \( 13 \) which would then re-combine to form the aminomethylene ester
\( 10 \). Referring to the classical work of the two Polonovskis, Craig et al.\(^9\) considered the exo-
thermic nature of the reaction also supportive of a free-radical mechanism.

In the course of a rather extensive study of the mechanism of the Polonovski rearrangement by
means of \( ^{18}O \) labeled acetic anhydride, Oae et al.\(^{11}\) first proposed that the reaction involves radi-
cal mechanism in solvent cage, in accordance with the fact that the acetoxy radical is extremely
unstable and short-lived. The facts that the reaction was not affected by the amount or kind of
solvents and the addition of radical scavengers, were thought strongly to suggest that the main
reaction proceeds through the "radical pair" process shown in Scheme 3.

Later in their studies,\(^{12}\) the Osaka group came to the conclusion that, in the rearrangements of \( \gamma \-
pycoline, \text{acridine, } \alpha, \text{N-diphenyl nitrone, lepidine, quinaldine and } 1 \)-methylisoquinoline \( N \)-oxides,
the reactions involve at least preponderately an ionic mechanism. It should be pointed out at this
point that, although an intramolecular ionic mechanism has often been favored to represent the
Polonovski rearrangement, using \( N^4 \)-oxides of \( 1,4 \)-benzodiazepines Šušnjić et al.\(^{13}\) unambiguously
showed the reaction to proceed in a non-concerted manner.

Conclusive evidence for the mechanism of the Polonovski reaction was obtained by the French group.
Studying the reaction by means of \( ^1H \) NMR spectroscopy, Michelot\(^{14}\) was able to identify several
crucial intermediates in favor of the mechanism outlined in Scheme 4. The mechanism is essentially...
Scheme 3

1st stage

\[
\begin{align*}
\text{RCH} - \text{N} & \rightarrow \text{RCH} - \text{N} + \text{CH}_3 \\
\text{Ac}_2\text{O} & \rightarrow \text{Ac}_2\text{O}
\end{align*}
\]

2nd stage

\[
\begin{align*}
\text{R}_2\text{C} & = \text{N} - \text{C} + 2\text{AcO}^- + \text{H}^+ \\
\text{R}_2\text{C} & = \text{N} - \text{C} + \text{AcO}^- + \text{H}^+
\end{align*}
\]

Scheme 4
identical with the one proposed by Huisgen et al. Further evidence to support this mechanism was gained by Volz and Kiltz, and Volz and Rucht, who succeeded in isolating the methyleneiminium species and carrying this intermediate on to give the Polonovski reaction products. Quite recently, Gartner has isolated and fully characterized also the acetoxammonium intermediates as well as the methyleneiminium species.

I-2 Acylating reagents - the modified Polonovski reaction

The original Polonovski reaction was conducted using acetic anhydride. It was observed that also other acylating agents can be used in the reaction. Cavé and Michelot pointed out that the acylating reagent has a dramatic effect on the regiochemical course of the Polonovski reaction. Thus, in the reaction trifluoroacetic anhydride and acetyl chloride liberate strong acids, which convert the esters of gem-amino alcohols to the corresponding iminium ion species.

In the modified Polonovski reaction, were the amine N-oxide is treated with trifluoroacetic anhydride, the diminished nucleophilicity and enhanced basicity of the trifluoroacetate ion disfavors the formation of the aminomethylene ester. Two formal pathways for the reaction can thus be expected:

i) an elimination reaction, in which only the C-H bond adjacent to the C-N bond is broken, and thus "normal" Polonovski intermediates are formed.

ii) a fragmentation reaction, in which the C-C bond adjacent to the C-N bond is cleaved. Examples of this mode abound in the literature, mainly in connection with the biomimetic syntheses of indole alkaloids.

The factors controlling the course of the modified Polonovski reaction, i.e. elimination vs. fragmentation, can be summarized as follows:

i) in the case of elimination, the most acidic proton a to the nitrogen is abstracted. It has not been explicitly studied whether the deprotonation occurs under kinetic or thermodynamic conditions but it seems that at least with trifluoroacetic anhydride as the acylating reagent, it is the thermodynamically most acidic proton that is cleaved. Thus the following reactions are observed (Equations 2, 3, 4, 5):

Chevolot et al. did in fact claim to have produced the iminium ion from . However, we have shown that the proponic acid derivative did lead to the endocyclic iminium ion. Furthermore, observation that the N-benzylpiperidine N-oxide forms the endocyclic iminium species, is also in contradiction with the explanation of the French group.

Gartner has also observed that, with acetic anhydride as acylating reagent, the course of the reaction on cyclohexyldimethylamine N-oxide is temperature-dependent: at low temperatures (-70°C) only kinetic deprotonation is observed, whereas higher temperatures (+80°C) lead to a
ii) in the case of fragmentation, the C-C bond to be cleaved must be antiperiplanar to the N-O bond. This reasoning is based on a consideration of the reaction in the light of Grob's rules for heteroatomic fragmentation reactions. A dextrous manifestation of this requirement was observed and exploited in the biomimetic synthesis of vinblastine-type alkaloids by Potier's group.

The question of cis/trans-disposition of the N-O bond and the C-H or C-C bond to be cleaved has received scanty experimental consideration. Although previously considered to proceed by cis-elimination, Lalonde et al. showed that in fact a trans-elimination took place in the Polonovski reaction. Thus, treatment of nupharidine with acetic anhydride led, probably via the corresponding iminium ion (note the orientation of the elimination with respect to the furyl)
substituent!)), to the enamine 22. With appropriately deuterated starting material they were able to verify that the proton abstracted is in fact anti-periplanar to the N-O bond.

Recently, Nakagawa et al.\textsuperscript{28} have studied the stereochemical requirements for the generation of an iminium ion from cyclic amine N-oxide. As starting materials, they used the cis and trans-indoloquinolizidines 23a and 23b. In the case of the cis-N-oxide 23a, either the strong acid present (CF$_3$COOH) could facilitate the isomerization of 25 or 26 to 24, or partial cis-elimination in (CF$_3$CO)$_2$O/CF$_3$CO$_2$H could lead directly to 24. Furthermore, the authors state that "treatment of either 23a or 23b with (CF$_3$CO)$_2$O in methylene chloride at room temperature afforded 24 in 50 % yield". Somewhat surprisingly, they end up concluding "that the reactions proceed probably by trans-elimination".\textsuperscript{28}
An important extension of the modified Polonovski reaction of sundry synthetic applications is the cyanotrapping method.\textsuperscript{23,29} In this method, the iminium ion 6, generated by means of the modified Polonovski reaction, is converted to the α-aminonitrile 27 simply by treatment of the reaction mixture with an aqueous solution of KCN. The α-aminonitrile 27 is itself an extremely versatile synthetic intermediate permitting both nucleophilic and electrophilic reactions to be conducted on the compound (some of the reactions are depicted in Scheme 5).

Scheme 5

Already prior to the unsaturated aminonitriles 27, the saturated aminonitriles of the type 28 have established their versatility as synthetic intermediates: the carbon atom α to the nitrogen being easily transformable to either nucleophilic or electrophilic at will, this functional unit provides easy access to a masked carbonyl equivalent or an iminium ion (through loss of cyanide ion). The functionality has also been shown to be dehydrocyanated to the corresponding enamine or decyanated reductively to the amine.\textsuperscript{30}

\begin{align*}
\text{Chart 3}
\end{align*}
In the piperidine series, we have shown that all three regioisomeric α-aminonitriles 29, 30, and 31 can be selectively prepared from the same starting material in short, high-yield syntheses thus giving access to a wide array of variously substituted piperidine synthons. We have also shown that the unsaturated aminonitriles of the type 27 are best alkylated at the 4-position using silyl enol ethers as nucleophiles and employing mild Lewis acid catalysis conditions.

II SYNTHETIC APPLICATIONS

Some synthetic applications of the Polonovski reaction have been reviewed but because of the limited scope or availability of these accounts, a more extensive and up-to-date review is presented below. The examples will be presented mainly in pictorial language, as flow charts.

As one can easily anticipate, most of the applications come from alkaloid chemistry. Thus, this chapter is divided in sections dealing with steroid alkaloids, indole alkaloids, simple piperidine derived alkaloids (including some frog toxins and adaline type alkaloids), benzodiazepines and finally other applications of more general interest. A special section is devoted to the synthetic transformations towards the important class of anti-tumor alkaloids of the vinblastine type.

II-1 Steroid alkaloids

The modified Polonovski reaction was first introduced to synthesis in connection with studies concerning steroid alkaloid transformations. Typically, N-methyldihydroparavallarine 32 was oxidatively deaminated to the corresponding 3-oxo compound. Also stereoselective hydroxylation at C-5 could be conducted on 5α steroidal 3α or 3β amides 33a or 33b.

II-2 Indole alkaloids

An unexpected fragmentation observed in the modified Polonovski reaction of 3α-N,N-dimethylamino-Δ5-androstene N-oxide led Ahond et al. to study the fate of N,N-dimethyltryptamine N-oxide under similar reaction conditions. The fragmentation found its applications in a partial synthesis of ervatamine-type alkaloids from those of vobasine type (dregamine, 34). The original idea presented by the French group had to await until Scott et al. in 1978 realized a transformation of stemmadenine 37 to vallesamine 38.

Hugel et al. observed a novel rearrangement of 1,2-dehydroaspidospermine N-oxide under the modified Polonovski reaction conditions.

An unexpectedly synthesized by Chevolot et al. in a straightforward manner.

A vincine 40 has been converted to craspidospermine 41. Using a somewhat altered strategy, the French group devised a total synthesis of the anti-tumor alkaloid ellipticine. The strategy consisting of six steps and giving a total yield of 18% is presented in Scheme 6.
Chart 4
Chart 5

Scheme 6
Mangeney has converted dregamine to $\Delta^{20}$-dregamine with acetic anhydride or acetyl chloride, in contrast to the modified Polonovski reaction of with trifluoroacetic anhydride or trifluoroacetyl acetate, where 20-epiervatamine was formed.

$\Delta^7$-Lysergic acid derivatives are conveniently prepared in a one-pot reaction from 9,10-dihydrolysergic acid methyl ester in fair yield.

Takano et al. have devised a new entry to the Strychnos alkaloids. Interestingly, treatment of the unsaturated amine oxide with trifluoroacetic anhydride led to the isolation of only the Strychnos framework. The formation of the alternative aspidospermatidine skeleton could not be observed.
VIN = 10-vindolinyl

Scheme 2
Recently, the French group has presented a synthesis of the ervitsine type compound \(^{44a}\), a total synthesis of (+)-20-epiuleine \(^{44b}\), a synthetic approach to the novel dimeric ervarfoline series \(^{44c,d}\) and a synthetic approach to the "inside" Corynanthe alkaloids \(^{44e}\), all strategies employing the α-aminonitrile synthon generated by means of the modified Polonovski reaction.

II-3 Vinblastine type alkaloids

The partial synthesis of the anti-tumor alkaloids of vinblastine-type was first realized by Potier et al. \(^{45}\) in 1975. This important body of alkaloids soon had several research groups working on it: those of Potier \(^{46}\), Kutney \(^{47}\), Ban \(^{48}\) and Atta-ur-Rahman \(^{49}\). Since two fine reviews by Potier \(^{46}\) have been devoted to the subject we shall leave it to present the synthesis of vinblastine \(^{51}\) itself in Scheme 7.

II-4 Piperidine analogues

The α-aminonitrile approach has led to strikingly many synthetic applications. Thus, a 2-spiro-substituted piperidine model \(^{52}\) of the frog toxin histrionicotoxin \(^{3}\) was synthesized using this approach. \(^{50}\)

Also the 2,6-dialkylpiperidines (+)-dihydropinidine \(^{53}\) and (+)-selenopsin A \(^{54,51}\), the poison-dart frog toxin gephyrotoxin model \(^{55}\) \(^{52}\) and the ladybug alkaloids \(^{56a}\) and \(^{56b}\) of the adaline series have recently fallen to synthesis by this methodology. \(^{53}\) The modified Polonovski reaction approach has also been employed by us in the synthesis of deoxygirgensonine \(^{57}\). \(^{23}\) The achievements of the French group have recently been reviewed by Husson. \(^{54}\)

![Chart 7](image-url)
II-5 Benzodiazepines

Since the Polonovski reaction of benzodiazepine N-oxides very closely resembles that of α,N-di-
diphenyl-nitrone it is worthwhile to notice that, according to Oae et al., the rearrangement occurs
via the competing bridged model (path a) and the cyclic migration model presented by Hanama et al.
(path b) (Scheme 8). Of the two paths, the bridged model seems to be the favored one and the re-
arrangement of the acetoxy group has been suggested to be the rate-determining step.

The Hoffmann-La Roche group has used the Polonovski reaction conditions to transform 1,4-benzo-
diazepine 4-oxide to pyrrolo[2,1-c]-1,4-benzodiazepine.

II-6 Other applications

One of the earliest applications of the Polonovski reaction was the synthesis of N-alkylpyrroles
from the corresponding Δ3-pyrrolidine N-oxides.1

A 2-ethylidene double bond at the 3-position in piperidines can be inverted to the natural E-con-
figuration by means of the modified Polonovski reaction (e.g. 60 to 61).

Wenkert et al. have suggested use of the modified Polonovski reaction for epimerisation of C-3
in geissoschizine. This approach gives highly improved yields over those of the previously em-
ployed oxidation-reduction sequence.

When the N-oxides of 62a and 62b were subjected to the modified Polonovski reaction followed by
aqueous KCN treatment, two regioisomeric α-aminonitriles were obtained. Compound 62a with equa-
torial methyl group at C-4 furnished expectedly the endocyclic α-aminonitrile 63, whereas 62b,
where the endocyclic iminium ion formation is blocked by the axial 4-methyl group, was transformed
to the 3-cyanomethyl benzazocine 64.
An ingenious but neglected use of the modified Polonovski reaction comes from an area rather distant to alkaloid chemistry, viz. that of macrolide antibiotics! The amino sugar moieties have thus been cleaved under conditions mild enough not to destroy the aglycone. The example chosen here is a very recent one from the degradation of 0-mycinosyltylonolide 65 to tytonolide 66 (Scheme 9).
III CONCLUSIONS

A trisubstituted nitrogen atom is an essential feature of alkaloids, alkaloid analogues and synthetic intermediates on the way to alkaloidal compounds. With the Polonovski reaction and its recent modifications the functionality is amenable to a plethora of useful synthetic transformations. As the examples in this Review show, alkaloid synthesis has already gained from the applications of this reaction. And as we have shown, its usefulness has spread beyond the area of alkaloid chemistry, inter alia to the important field of macrolide chemistry.

The mechanistic basis of the modified Polonovski reaction, and the variables governing its regiochemical outcome, are at present sufficiently well understood so that the reaction can be included in the chemical arsenal of the synthetician working in natural products field.

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REFERENCES AND NOTES

3. The reaction is also known as the Polonovski-Potier reaction.
6. Wenkert did consider an alternative, concerted reaction mechanism, but rejected this hypothesis as a general one, since this would lead to iminium ions at bridgehead position [cf. M. Polonovski, M. Darmon and P. Rajzman, C.R. Acad. Sci. Paris, 1952, 234, 108].
   c) S. Tamagaki, S. Kozuka and S. Oae, ibid., 1970, 26, 1795.


   b) M. Hanama, B. Umesawa, Y. Goto and K. Noda, ibid., 1960, 8, 967.
    1979, 101, 6742.

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