

The Unusual Deacylation Reaction

Shota Samsoniya^{*}, Nana Targamadze^{}, Dali Kajrishvili^{**},
Lia Bobokhidze^{**}, Nana Megrelishvili[§], Ioseb Chikvaidze^{**}**

^{*}Academy Member, Scientific Research Institute of Organic Synthesis, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

^{**}Scientific Research Institute of Organic Synthesis, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

[§]Faculty of Exact and Natural Sciences, A. Tsereteli State University, Kutaisi, Georgia

The unusual deformylation (deacylation) reactions of some indole aldehydes under different conditions were studied. It is shown that this reaction easily run in excess of ethylene glycol at temperature of 50-150°C and does not require the participation of acid catalysts and that reaction is facilitated by donor substituents in the aromatic ring. It was shown that unsubstituted and strong acceptor containing aromatic oxo-compounds and isomeric nitrobenzaldehydes does not react even in extreme conditions, while p-nitroacetophenone is included in the homocrotonic condensation.
© 2020 Bull. Georg. Natl. Acad. Sci.

Deformylation, deacylation, indole, phenylindole

3-formylindoles (Generally acylindoles) are widely used for synthesis of the important indole analogues. In the process of studying the condensation reaction of the carbonyl group of 2-aryl-3-formylindoles, which was conducted under classical conditions typical for 3-formylindole (heating a mixture of aldehyde, CH-acid and ethylene glycol) [1], It was noticed that the substrate did not enter into a condensation reaction at a temperature of 150°C. From the reaction products 3-unsubstituted indole products were separated, i.e. compounds from which the initial 2-aryl-3-formylindoles were obtained. Thus a new, unusual deformation reaction was discovered [2,3]. According to the authors, deformylation occurs with the formation of cyclic acetals and their subsequent decomposition.

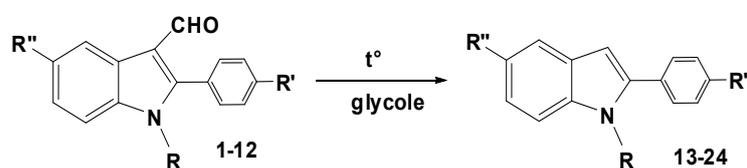
Deacylation (decarbonylation, deformylation) reactions of aromatic and heterocyclic compounds are known for a long time - in 60% KOH (100°C), HClO₄ and conc.H₂SO₄, in some cases, NaOH, CaCl₂, NaH, toluene sulfuric acid (TsOH) and other reagents are also used. Photochemical deformation reaction is described [4]. The catalyzed deformylation and deacetylation reactions of 2- and 3-formyl (acetyl) pyrroles were described by Moon and Wade [5] and others [6,7].

The reaction is carried out by heating a mixture of acetyl product and catalyst with a molar ratio of 1/0.1 in an excess of ethylene glycol, or by boiling the acetyl product, catalyst and ethylene glycol with a molar ratio of 1/0. 1/2 in a benzene. p-Toluenesulfonic acid or chloric acid [5,6], as well as boron trifluoride in acetic acid, were used as

catalysts [6]. The debenzoylation reaction of 3-benzoyl-2-phenylindoles is described [5]. It should be noted that deacetylation of 4-acetyl-1-phenyl-5-methylpyrazole is completed within 48 hours and requires a triple excess of catalyst [5]. It is also difficult to deacetylate the isomeric dimethoxyacetophenones (TsOH, chloric acid), and acetophenone and its monomethoxine derivatives do not react in this reaction at all [5]. The deformylation reaction of indol-3-yl- and azaindol-3-ylaldehydes with the participation of anthranilamide and acid catalyst are also described [7].

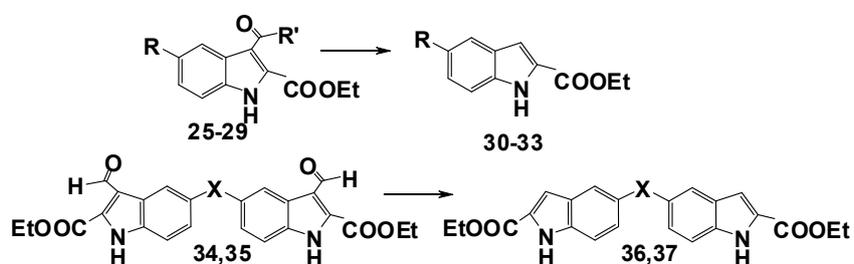
reactions increases. This refers especially of acidophobic systems such as π -excess heterocycles and similar aromatic compounds. In previously described cases [5-7] the substituent groups in the initial acyl molecules do not belong to strong acceptors (the exception is the ester group).

To our point of view, donor substitutes may reduce the resistance of intermediate cyclic acetals, so these reactions was conducted with aromatic and heteroaromatic oxo compounds containing unsubstituted and strong acceptor groups, e.g., nitro products.



1,13 R=R'=R''=H; 2,14 R=R'=H, R''=CH₃; 3,15 R=R'=H, R''=Br; 4,16 R=R''=H, R'=Br;
5,17 R=R''=H, R'=OCH₃; 6,18 R=R''=H, R'=C₆H₅; 7,19 R=R''=H, R'=CH₂-C₆H₅;
8,20 R=R''=H, R'=CH₂-CH₂-C₆H₅; 9,21 R=CH₃, R'=R''=H; 10,22 R=R''=CH₃, R'=H;
11,23 R=CH₃, R''=H, R'=Br; 12,24 R=CH₃, R''=H, R'=OCH₃;

Scheme 1. 2-aryl-3-formylindoles (1-12) deformylation.



25,30 R=R'=H; 26,31 R=CH₃, R'=H; 27, 32 R=Br, R'=H;
28,33 R=S-C₆H₄NO₂(p), R'=H; 29 R=S-C₆H₄NO₂(p), R'=CH₃;
34,36 X=CH₂; 35,37 X=O

Scheme 2. 3-formylindoles (25-29) and diformylindoles deformylation.

The deformylation reaction we carried out is more unambiguous than the deformylation reaction described by Moon, Wade [5] and others [6,7]. We found that in the presence of strong reagents, especially in conditions of their abundance, even at relatively low temperatures, the number of side

We studied the deformylation reaction of some indole aldehydes under different conditions (Schemes 1-3) and obtained significant results are discussed below.

Deformylation of compounds 1-3 and 6-8 is described in our previous publications [2,3]. The

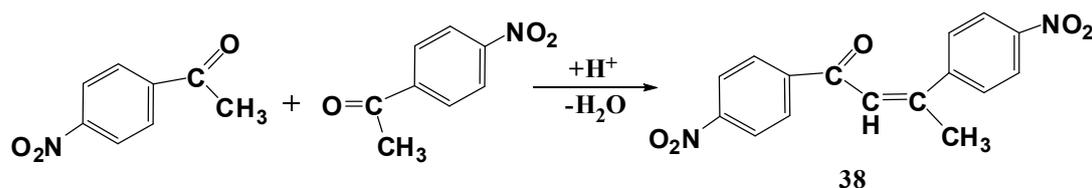
deformylation of the rest of aldehydes presented on the schemes are carried out at 50-100°C without the catalyst in ethylene glycol. The influence of substitution groups is almost imperceptible. Deformylation at temperatures above 100°C is more intense, although the proportion of side processes also increases. A similar process of deformylation takes place in glycerin. Presumably, deformylation under heating conditions is promoted by the increased acidic properties of polyatomic alcohols.

Compounds 1-12, 25-29, 34 and 35 similarly react with toluenesulfonic acid in the reaction area described by Moon and Wade [5] with catalysts. Deformylation does not occur in monoatomic alcohols (ethanol, butanol-1, hexanol-1, cyclohexane). Deformylation is not also observed in a high-boiling, non-polar solvents (toluene, o-xylol, isopropylbenzene).

Deformylation reaction of N-methyl derivatives (9-12) with the highest yield is carried out both in ethylene glycol and with the participation of toluenesulfonic acid. There are almost unnoticeable side reactions, and the degree of conversion is determined only by the time factor, the latter primarily refers to bisindole dialdehydes (34, 35).

It should be noted that 3-acyl-2-ethoxycarbonyl-5-p-nitrophenylthioindoles (28, 29) are not included in the deacylation reaction.

In order to study how these reactions would occur in the case of unsubstituted and acceptor group containing aromatic aldehydes under the alternative conditions described above we studied the possibility of deformylation and deacetylation reactions of unsubstituted and acceptor group containing aromatic aldehydes, on the examples of benzaldehyde, m-nitrobenzaldehyde and p-nitroacetophenone. We tried all the conditions described above: heating to 50-150°C in ethylene glycol, boiling (198°C) without catalyst or with toluene sulfuric acid, the equimolar ratio of the latter or a tenfold excess. The reaction did not occur in no mentioned cases. This was confirmed both by TLC (thin-layer chromatography) and by separation of the starting compounds from the reaction area. To separate the initial m-nitrobenzaldehyde and p-nitroacetophenone, the reaction area was diluted with water in a ratio of 1:10 and formed precipitate was filtered and washed with water until the neutral reaction. This way, almost pure starting materials were obtained. It should be noted that during the boiling of p-



Scheme 3. Homocondensation reaction of p-nitroacetophenone.

In our mind, N-methyl group increases the resistance of the heterocycle towards the high temperatures and strong acid environments. Deformylation of N-unsubstituted aldehydes (1-8) under similar conditions is more difficult due to their lower stability. In all cases the advantage of so-called "unusual deformylation" reaction conditions is obvious.

nitroacetophenone in the presence of toluenesulfonic acid in ethylene glycol the condensation reaction takes place and a new solid substance is formed, presumably, 1,3-bis (p-nitrophenyl) butene-2-on-1 (38) (scheme 3) an analogue of the condensed product described by M.W. Moon, R. A. Wade [5]. The separation and

description of this substance was not included in our work plan.

Experimental data confirm the contributing effect of donor substituents on the deformation reaction (generally deacetylation), in contrast to the influence of acceptor substituents, in the presence of which the reaction does not occur at all.

This reaction does not occur in unsubstituted aromatic and heteroaromatic oxo compound. The deacylation reaction also does not include 3-acyl-2-ethoxycarbonyl-5-p-nitrophenylthioindoles (28, 29).

The data of our experiment highlight the advantages of so-called "unusual deformation reaction" conditions over the classical ones.

Experimental Part

All reactions and the purity of the compounds were monitored by TLC on silica gel Al-foils and Silufol UV 254 plates. For column chromatography as a sorbents we used silica gel with particle sizes of 100-250 and 100-160 μm . Indole products and corresponding aldehydes were identified by R_f (on TLC) and melting point compared to the literature data (mixed sampling method).

General Methodology for Receiving Formyl-Indole Derivatives (1-12,25-29, 31,32).

2.62 g (0.036 mol) freshly distilled DMF cooled to -5°C by dropwise is added 1.38 g (0.009 mol) POCl_3 under stirring and cooling. The reaction mixture is stirred half an hour at cooling and then 1 hour at room temperature. The resulting complex is again cooled to 0°C and added solution of (0.003 mol) indole derivatives in DMF (5-10 ml). The mixture is heated to room temperature or to 65°C and stirred

for 2-3 hours, then it cooled and under the constant stirring 100g of finely crushed ice is added. Obtained yellow solution is filtered and is added conc. NaOH solution to the pH 12 and formed precipitate is filtered, washed with water until the neutral reaction and dried.

General Method of Deformylation.

Method A. 30ml of distilled ethylene glycol is added to 0.001 mole of oxo compound and heated up to $50-100^{\circ}\text{C}$ under stirring, for 2-3 hours. Then the solution is cooled, diluted with 300ml. of cold water and formed precipitate is filtered, washed with water and dried. Deformylation product is purified by crystallization or by column chromatography.

Method B. 0.001 mol of oxocompound is added to 100ml of benzene or toluene, 5-10ml of freshly distilled ethylene glycol and 0.001-0.01 mole of toluene sulfuric acid. The reaction mixture is boiled in a flask equipped with dean stark trap. After the reaching a constant level of water in Dean-Stark receiver the boiling is continued for another 2 hours. The solution is then cooled, washed in a separatory funnel with water until a neutral reaction, and dried over anhydrous CaCl_2 . The solvent is evaporated in a rotary evaporator to dry residue. Deformation products are purified by crystallization or chromatography.

This work was financially supported by Shota Rustaveli National Science Foundation (SRNSF) of Georgia grant FR17_431, Project title: Potential Intercalators and Fluorescent Biomarkers on the Basis of Indole-Containing Heterocycles.

ორგანული ქიმია

უჩვეულო დეაცილირების რეაქციის შესახებ

შ. სამსონია*, ნ. თარგამაძე**, დ. ყაჯრიშვილი**, ლ. ბობოხიძე**,
ნ. მეგრელიშვილი‡, ი. ჩიკვაძე**

*აკადემიის წევრი, ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, თბილისი, საქართველო

**ივანე ჯავახიშვილის სახ. თბილისის სახელმწიფო უნივერსიტეტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, თბილისი, საქართველო

‡ა. წერეთლის სახელმწიფო უნივერსიტეტი, ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი, ქუთაისი, საქართველო

შესწავლილია ზოგიერთი ინდოლური ალდეჰიდის უჩვეულო დეფორმირების (დეაცილირების) რეაქციის მიმდინარეობა სხვადასხვა პირობებში. ნაჩვენებია, რომ ეს რეაქცია ადვილად მიმდინარეობს ჭარბ ეთილენგლიკოლში 50-150°C-ზე და არ საჭიროებს მჟავა კატალიზატორების მონაწილეობას. ამ რეაქციას ხელს უწყობენ დონორული ჩამნაცვლებლები. ნაჩვენებია, რომ ჩაუნაცვლებელ და ძლიერი აქცეპტორების შემცველ არომატულ ოქსო-ნაერთებში იზომერულ ნიტრობენზალდეჰიდებში ეს რეაქცია არ მიმდინარეობს მკაცრ პირობებშიც კი, ხოლო პ-ნიტროაცეტოფენონი შედის ჰომოკროტონულ კონდენსაციაში.

REFERENCES

1. Jungietu G.I., Budilin V.A., Kost A.N. (1975) Preparativnaia khimiia Indola, 264 p. Kishiniov (in Russian).
2. Samsoniya Sh.A., Chikvaidze I. Sh., Narindoshvili T.G. (1999) New deformylation reaction of 2-substituted-indole-3-aldehydes. *Georgian Engineering News*, 2: 120-121 (in Russian).
3. Chikvaidze I. Sh., Samsoniya Sh. A., Narindoshvili T. G., Kobakhidze N. V. (2000) Deformylation of some 2-substituted indole-3-aldehydes. *Chemistry of Heterocyclic Compounds*, 36 (11): 1346 (www.Kluweronline.com/issn/0009-3122/contents).
4. Mishchenko G. L., Vatsuro K. B. (1992) Sinteticheskie metody organicheskoi khimii. 440 p. (in Russian).
5. Moon M.W., Wade R. A. (1984) Deacylation of Pyrrole and other aromatic ketones. *J. Org. Chem.* 49: 2663-2669.
6. Smith K. M., Miura M., Tappa H. D. (1983) Deacylation and deformylation of Pyrroles. *J. Org. Chem.* 48: 4779-4781.
7. Yadav R. R., Battini N., Mudududdla R. et all. (2012) Deformylation of indole and azaindole-3-carboxaldehydes using anthranilamide and solid acid heterogeneous catalyst via quinazolinone intermediate. *Tetrahedron Letters*, 53 (17): 2222-2225 DOI:10.1016/j.tetlet. 2012.02.079.

Received July, 2020