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HETEROCYCLES IN FOCUS

Synthesis of 6-(aryldiazenyl)-4*H*-chromene derivatives (microreview)

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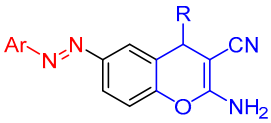


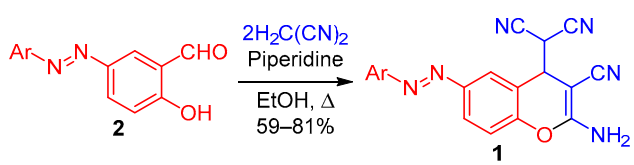
The microreview summarizes the data published over the last 10 years on the methods of preparation and properties of 6-(aryldiazenyl)-4*H*-chromenes, a new promising class of compounds incorporating the azo and 4*H*-chromene fragments in their structure. The material is systematized according to the structure of the starting reagents.

Introduction

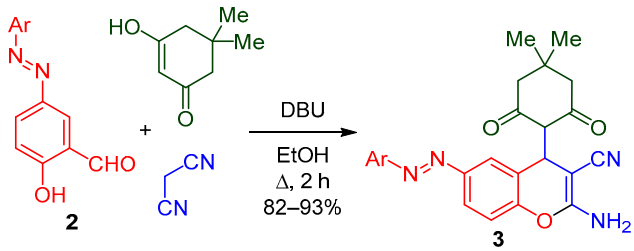
Functionally substituted chromenes, in particular 2-amino-4*H*-chromene-3-carbonitriles, represent one of the most popular classes of heterocyclic compounds. The great interest in the chemistry of substituted chromenes is reflected in an impressive number of recent reviews[1–15] and is owing to the exceptional accessibility of 2-amino-4*H*-chromene-3-carbonitriles and the wide spectrum of their biological activity. Azo compounds represent another well-known and readily available class of compounds. Despite their long history, azo compounds are still the object of close attention as biologically active molecules,[16,17] as markers in biomedical research,[19–21] and also because of their unique photochemical and optical properties.[22–24] In recent years, a number of studies have been dedicated to the synthesis and study of the properties of substituted 6-(aryldiazenyl)-4*H*-chromenes, a new class of compounds that are of interest both for their optical properties and possible biological activity. The simultaneous presence in their molecule of 4*H*-chromene and azo pharmacophore fragments in some cases results in a synergistic effect. This microreview presents the most significant studies of the chemistry of 6-(aryldiazenyl)-4*H*-chromenes published over the last 10 years.

Synthesis on the basis of 5-(aryldiazenyl)-2-hydroxybenzaldehydes

The products of azo coupling of aryldiazonium salts with salicylic aldehydes seem to be the most convenient starting reagents for the preparation of target arylazochromenes. Thus, chromenes **1** were obtained by the reaction of aldehydes **2** with 2 equiv of malononitrile in the presence of piperidine.[25,26] Compound **1** (Ar = 4-ClC_6H_4) possesses a pronounced antibacterial and fungicidal activity.[26]



When malononitrile and dimedone were introduced into the reaction instead of 2 equiv of malononitrile, chromenes **3** were formed which showed *in vitro* anticancer activity on MCF-7 cells.[27]



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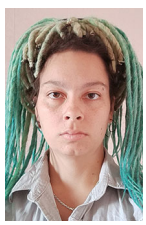
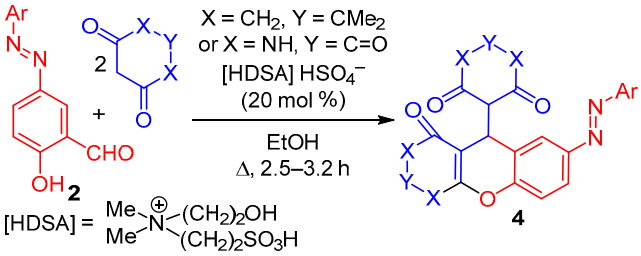


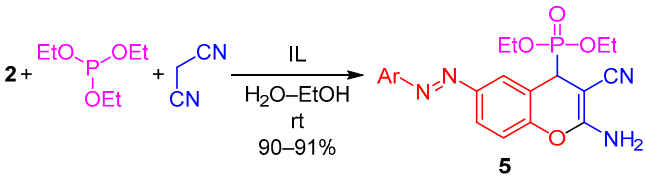
Ekaterina A. Varzieva was born in Nalchik in 1994 and is currently a graduate student at the Department of Organic Chemistry and Technology of the Kuban State University. Her research interests include chemistry of heterocyclic compounds, chemistry of organosilicon compounds, epoxy compounds.

Synthesis on the basis of 5-(aryldiazenyl)-2-hydroxybenzaldehydes (continued)

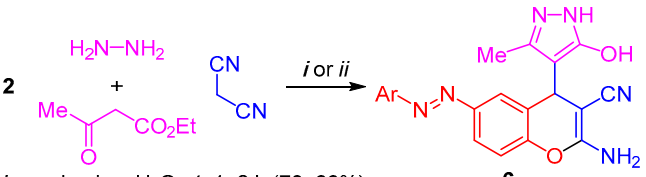
When malononitrile is replaced by dimedone,[28] barbituric acid,[28] or 4-hydroxycoumarin,[29] 4*H*-chromenes are also formed as the products. Azo compounds **4** obtained in this way exhibit[28] moderate anti-inflammatory and antioxidant activity.



The three-component condensation of $H_2C(CN)_2$, $P(OEt)_3$, and aldehydes **2** in the presence of basic ionic liquids (IL) led to (4*H*-chromen-4-yl)phosphonic acid esters **5**.[30] Molecular docking results for the BCL2 apoptosis regulator indicated a potential anticancer activity of compounds **5**.



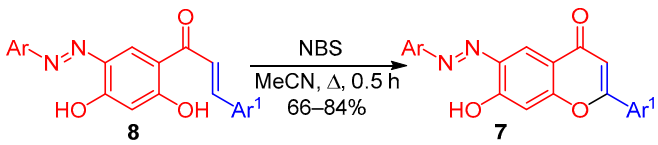
A multicomponent synthesis of 4-pyrazolyl-4*H*-chromenes **6** by the reaction of aldehydes **2**, malononitrile, hydrazine, and ethyl acetoacetate in the presence of meglumine in H_2O[31] or by a mechanochemical reaction in the presence of Fe_3O_4-based magnetic nanoparticles[32] was described. It is likely that the use of such exotic catalysts is not strictly necessary; however, this is the sole example of the synthesis of chromenes **6** in the literature. Compounds **6** exhibit intense fluorescence with an emission maximum at 582–586 nm.[31]



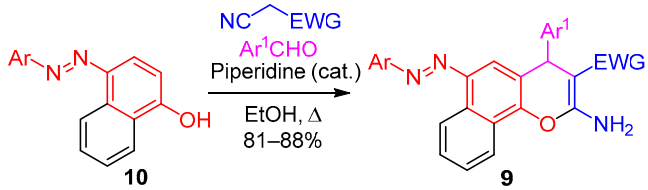
i: meglumine, H_2O, rt, 1–2 h (78–88%)
ii: Fe_3O_4@SiO_2@KIT-6-NH_2@Schiff base complex nanoparticles, rt, 10–15 min (87–92%)

Synthesis on the basis of 4-(aryldiazenyl)phenols

Cyclization reactions based on 4-(aryldiazenyl)phenols are a convenient alternative to the approaches based on 5-(aryldiazenyl)salicylic aldehydes discussed above. Despite the exceptional accessibility of phenol-based azo coupling products, the examples of the syntheses of 4*H*-chromenes based on 4-(aryldiazenyl)phenols are few and are published almost exclusively recently. Thus, derivatives of flavone **7**, which have a pronounced antioxidant and antibacterial effect, were obtained by oxidative cyclization of unsaturated ketones **8**.[33]

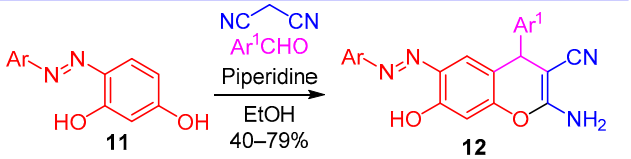


Intensely colored 4*H*-benzo[*h*]chromenes **9** were synthesized by the reaction of aldehydes, active methylene nitriles, and 4-[(4-ethoxyphenyl)diazenyl]-α-naphthol **10**.[34] Compounds **9** also exhibit pronounced antimicrobial and antitumor activity.

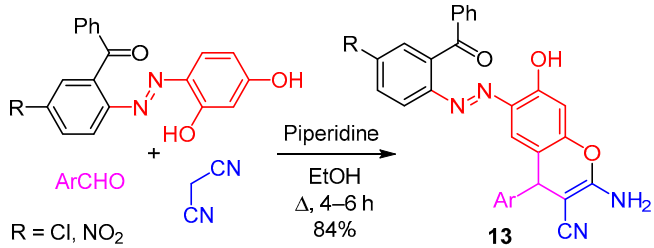


Ar = 4-$EtOC_6H_4$; EWG = CN, COOEt

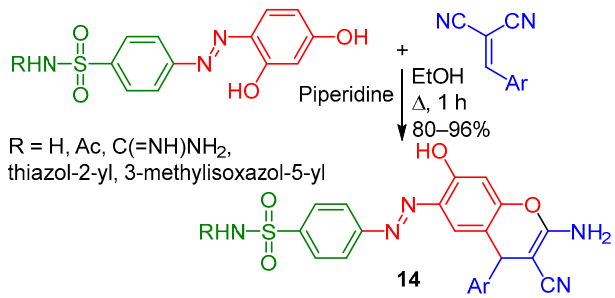
The first examples of the use of 4-(aryldiazenyl)resorcinols **11** in the synthesis of 6-(aryldiazenyl)-4*H*-chromenes appeared in the literature in 2017.[35,36] Products **12** have antibacterial, fungicidal, and anticancer effects.



Further modification of the substituents led to the preparation of azo compounds **13** with an improved pharmacological profile.[37]

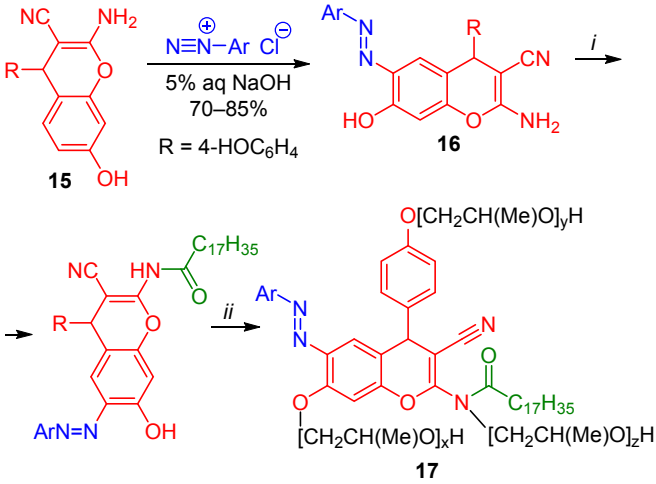


The introduction of a zinc-binding sulfamide fragment into the diazo component and subsequently into the resorcinol derivative led to azosulfonamides/4*H*-chromenes **14**, which are strong inhibitors of class I zinc-dependent histone deacetylases with anticancer activity.[38] Compounds **14** have absorption maxima in the range of 387–445 nm and also show antimicrobial activity.



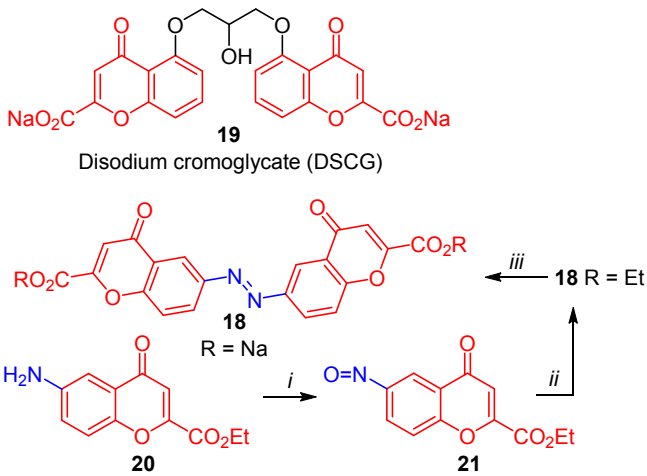
Synthesis on the basis of 4*H*-chromenes

Upon a possibility of modification, 4*H*-chromenes can also serve as starting compounds for the preparation of 6-(aryldiazenyl)-4*H*-chromenes. For example, 7-hydroxy-4-(4-hydroxyphenyl)-4*H*-chromene **15** underwent regio-selective azo coupling to form azochromenes **16** which exhibit antioxidant activity.[39] Sequential treatment with stearoyl chloride and excess propylene oxide gave colored surfactants **17** suitable for use as antioxidants for lubricating oils.



i: $C_{17}H_{35}C(O)Cl$, Et_3N, Me_2CO
ii: propylene oxide, KOH, N_2, 1–10 h

The preparation of azochromene **18**, an analog of sodium cromoglycate **19**, an anti-allergic and anti-asthma chromene drug, was described.[40] The presence of an azo bridge allows *cis*/*trans* photoisomerization and controlled inhibition of mast cell activation (only the *cis*-form is biologically active). It was noted that the novel photoswitchable inhibitor **18** has a much higher activity than the original dichromene **19**. The key step in the preparation of azochromene **18** is the reaction of 6-aminochromene **20** and 6-nitrosochromene **21**.



i: Oxone, CH_2Cl_2–H_2O, rt, 2 h (70%)
ii: **20**, AcOH, rt, 48 h (43%); *iii*: EtOH, NaOH, Δ, 2 h (91%)

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