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Mendeleev Commun., 2022, **32**, 678–679

Mendeleev Communications

Synthesis of 7-oxindolylidene-3a,9a-diphenylimidazothiazolo[2,3-*c*][1,2,4]triazines by skeletal rearrangement of their [3,2-*b*]-fused isomers

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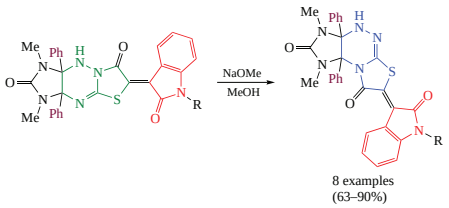
DOI: 10.1016/j.mencom.2022.09.037

Previously unavailable 7-oxindolylidene-1,3-dimethyl-3a,9a-diphenylimidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazines were obtained in 63–90% yields by skeletal amidine rearrangement of the thiazolo-triazine system in the corresponding imidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazines on treatment with sodium methoxide.



Keywords: oxindolylidene derivatives, imidazothiazolotriazines, thiazolidinones, skeletal amidine rearrangement, isatin.

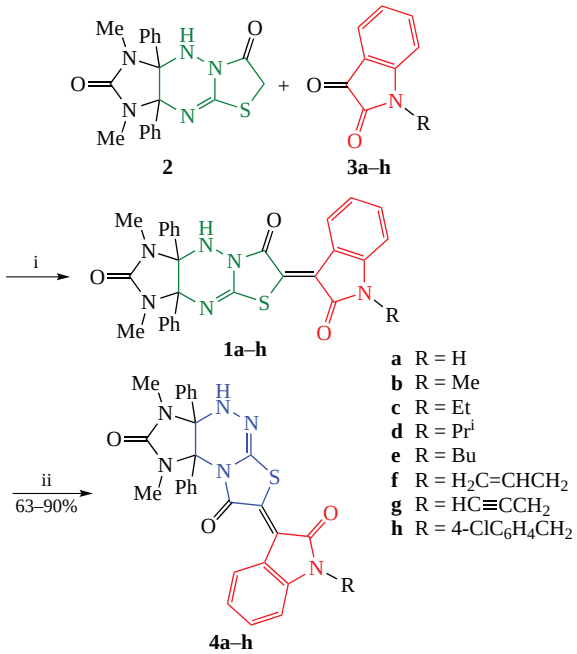
The heterocyclic thiazolidin-4-one system is a privileged structure in the modern medicinal chemistry that manifests a broad spectrum of biological activity and wide opportunities for its modification.[1–5] Many biologically active thiazolidin-4-ones and their hetero-annulated analogues are products of aldol condensation with isatins that are promising compounds for application as antibacterial, fungicide and antiviral drugs and in cancer therapy.[4–9] Moreover, further conjugation of oxindolylidene derivatives of thiazolidin-4-ones with the pyrrolidine ring in 1,3-dipolar cycloaddition reactions is motivated by the creation of spiro- and dispirocyclic oxindole derivatives,[10,11] analogues of a number of natural alkaloids,[12–14] and an important class of spiroindolinone anticancer drugs[15–18] based on them.

Previous systematic *in vitro* studies on the antitumor activity of oxindolylidene derivatives of imidazo[4,5-*e*]thiazolo[3,2-*b*]-[1,2,4]triazine and imidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine made it possible to identify a number of compounds with high cytotoxicity against some human tumor cell lines.[19–21] Imidazothiazolo[2,3-*c*]triazine derivatives obtained by skeletal isomerization of the corresponding [3,2-*b*]-fused isomers in methanol in the presence of KOH showed higher activity.[19–23] That method was successfully used to obtain various imidazo[4,5-*e*]thiazolo[2,3-*c*]triazines but was not good for synthesizing similar compounds containing two phenyl substituents at positions 3a,9a of the tricyclic system.[19,24]

In this work, we suggest an efficient procedure to perform the rearrangement of such diphenyl-substituted substrates **1a**–**h** into oxindolylidene derivatives of 1,3-dimethyl-3a,9a-diphenyl-imidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazines by the application of a stronger base, namely, sodium methoxide (Scheme 1). The initial compounds **1a**–**h** were obtained in 74–93% yields by the condensation of methylene-active 1,3-dimethyl-3a,9a-diphenyl-imidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine **2** with isatins **3a**–**h** under basic catalysis conditions (KOH) by a reported procedure.[24] The rearrangement of compounds **1a**–**h** into the target compounds **4a**–**h** was performed in boiling methanol. In fact, isomerization of compound **1a** into **4a** did not occur even with excess KOH (up to 2 equiv.). The best yields of compounds **4a**–**h** (63–90%) were obtained using sodium methoxide as the base (see Scheme 1 and Table S1 of Online Supplementary Materials).

The condensation product of imidazothiazolotriazine with unsubstituted isatin **1a** and compounds containing allyl, propargyl or benzyl substituents at the nitrogen atom of the oxindole moiety **1f**–**h** easily underwent isomerization in 15–30 min in the presence of 0.5 equiv. NaOMe, whereas the rearrangement of compounds with alkyl substituents **1b**–**e** required the application of 1 equiv. of sodium methoxide, or prolongation of the reaction time to 1 h.

The structure of compounds **4a**–**h** was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy and high resolution mass spectrometry. The structure of compound **4f** was also confirmed by ^{1}H-{^{15}N} HMBC and ^{15}N CP MAS NMR (solid-phase



Scheme 1 *Reagents and conditions*: i, KOH, MeOH, reflux; ii, NaOMe (0.5 or 1 equiv.), MeOH, reflux, 15–60 min.

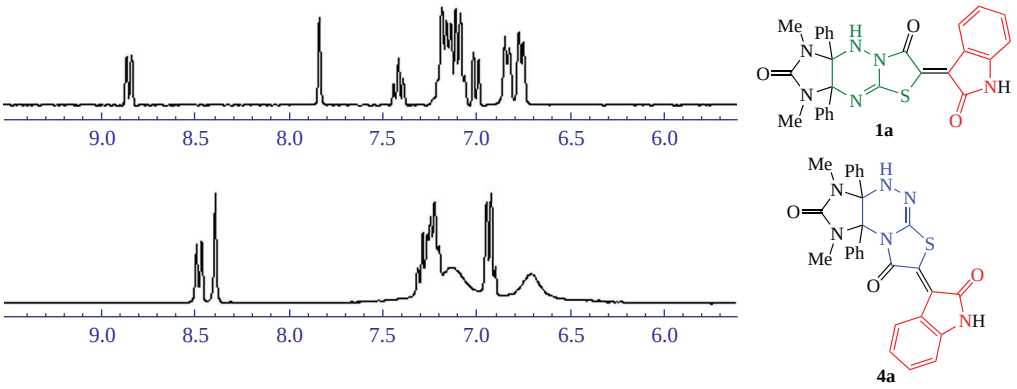
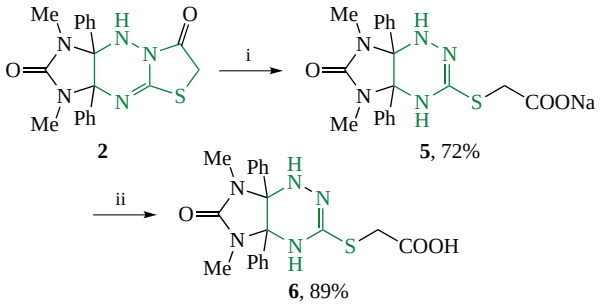


Figure 1 Fragments of the ^{1}H NMR spectra of isomeric compounds **1a** and **4a** in the range of 5.6–9.5 ppm.



Scheme 2 *Reagents and conditions*: i, NaOMe, MeOH, reflux; ii, HCl, H_2O.

^{15}N NMR by cross-polarization with rotation at the magic angle, see Online Supplementary Materials).[24] The ^{1}H NMR spectra of imidazothiazolotriazine derivatives with angular structure **4** manifest broadening of the signals of *ortho*- and *para*-positioned protons, instead of a system of characteristically split proton signals of two phenyl substituents observed in the spectra of linear structures **1** (Figure 1). The strong downfield shift of the signal of the C(4′)–H hydrogen atom in comparison with the signal positions of the other protons in the oxindole moiety is explained by the proximity of the oxygen atom in the carbonyl group of the thiazolidine ring and indicates that the exocyclic double bond has the *Z*-configuration in the parent compounds **1**[24–26] that is preserved upon rearrangement into isomers **4**.

A study on the possibility of performing the rearrangement of tricyclic compound **2** showed that its treatment with an equivalent amount of sodium methoxide resulted in irreversible opening of the thiazolidine ring, as it was previously observed for related structures in the presence of bases,[27,28] to give sodium salt **5** (Scheme 2) that was isolated from the reaction mixture in 72% yield. Acidification of its aqueous solution with hydrochloric acid affords thioglycolic acid derivative **6**.

In summary, we expanded the applicability of the thiazolotriazine moiety rearrangement in the presence of bases and developed an efficient synthesis of new oxindolylidene derivatives of imidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine from readily available 1,3-dimethyl-3a,9a-diphenylimidazo[4,5-*e*]-thiazolo[3,2-*b*][1,2,4]triazine derivatives.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.037.

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Received: 31st March 2022; Com. 22/6850