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PALLADIUM-CATALYZED CYCLIZATION REACTIONS OF 3-PROPARGYLTHIO-1,2,4-TRIAZIN-5(2H)-ONES TO THIAZOLO-1,2,4-TRIAZINONES

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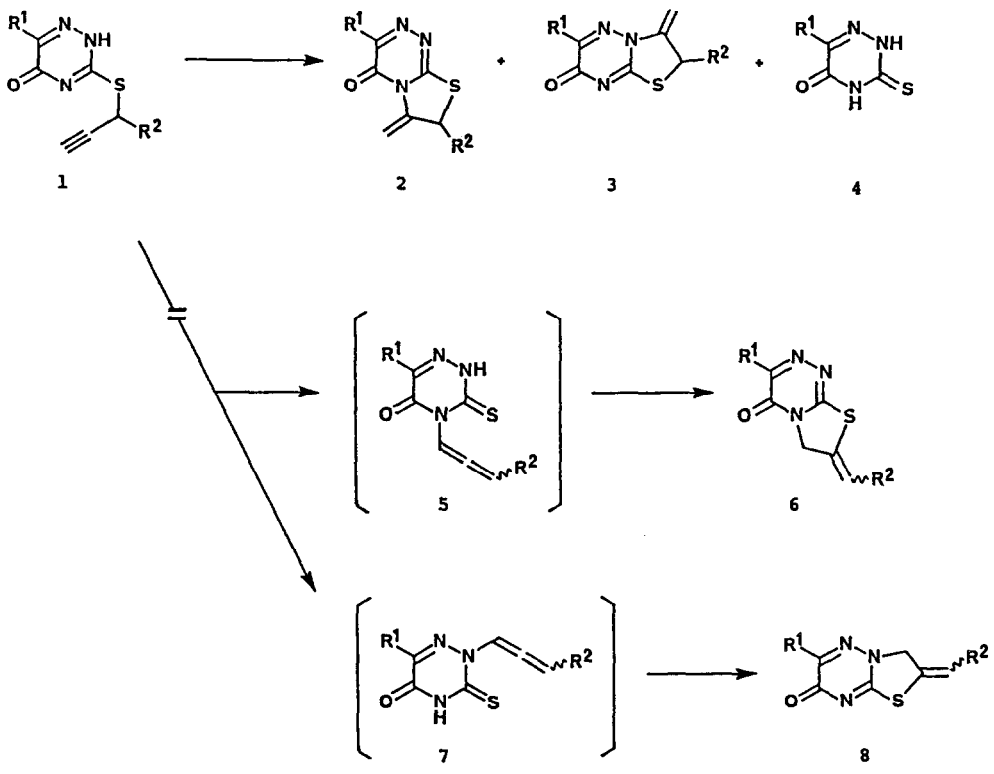
Abstract: Selective transformation of 3-propargylthio-1,2,4-triazin-5(2H)-ones (1) to 6-methylene-6,7-dihydro-4H-thiazolo[2,3-c][1,2,4]-triazin-4-ones (2) and 3-methylene-2,3-dihydro-7H-thiazolo[3,2-b]-[1,2,4]triazin-7-ones (3) is performed under the conditions of Pd(II) salt or sodium hydroxide catalysis, respectively.

Many efforts have been devoted to the preparation of a variety of heterocyclic compounds by making use of Pd-catalyzed intramolecular functionalization of olefins as the ring-forming step.[1] Such a functionalization of acetylenes seems to be very promising because the remaining double bond may be utilized for further transformations after cyclization.[2] In this communication, we describe a novel transformation of 3-propargylthio-1,2,4-triazin-5(2H)-ones 1 to thiazolo-1,2,4-triazinones 2 and 3 (Scheme I). The former regioisomer, 6-methylene-6,7-dihydro-4H-thiazolo[2,3-c][1,2,4]triazin-4-ones 2, was obtained selectively or exclusively by catalysis with a palladium(II) salt, and the latter isomer, 3-methylene-2,3-dihydro-7H-thiazolo[3,2-b][1,2,4]triazin-7-ones 3, by the catalysis of sodium hydroxide.

Results, together with the reaction conditions for five kinds of 1, are summarized in Table I. As seen from this Table, 2-5 mol% of a Pd(II) salt is sufficient for the complete cyclization of 1. The reaction could be undertaken both in aprotic and protic solvents at their refluxing temperatures. Without palladium, no reaction took place and the starting material was recovered.[3] Generally Pd-catalyzed reaction provides 2 as a main product together with small amounts of 3 and depropargylated product 4. There seems to be a general trend that the product 4 is formed in large amounts in the cases where the reactions are reluctant (entries 1 and 5). The methyl substituent as R^2 accelerates the reaction and diminishes the formation of 4 (cf. entries 7 and 9).

The sodium hydroxide catalyzed cyclization of 1, on the other hand, proceeds cleanly to provide 3 as a single product, when the reaction was stopped at an appropriate conversion. Further reaction caused decomposition of the product. Both the exclusive cyclization on the N-2 nitrogen atom

Scheme I



(entries 2, 4 and 8), and the exceptional concomitant cyclization on N-4 in 1c (entry 6), are reminiscent of the alkylation of 3-methylthio-1,2,4-triazin-5(2H)-ones with alkyl halides under basic conditions.[4]

The determined structures of 2 and 3 (and not 6, 8 or others, Scheme I) clearly indicate that the Pd-catalyzed isomerization of 1 to 2 and/or 3 proceeds via a direct attack of the N-4 and/or N-2 nitrogens, respectively, to the acetylenic triple bond activated by the coordination of palladium(II). This dramatic change of the reaction pathway compared with the Pd-catalyzed S → N allylic rearrangement of 3-allylthio-1,2,4-triazin-5(2H)-ones[5] may be mainly due to the high reactivity of acetylenes toward nucleophiles[6] and also due to an unsuitable conformation in 1 for a [3,3]sigmatropic rearrangement[7] (Scheme I).

Structures of 2 and 3 were distinguished from their physical and spectral data. In the ^{1}H NMR spectra of 2, the exo methylene proton syn to the C-5 carbonyl appeared downfield by ca. 1.3 ppm compared with the anti proton, while the methylene protons in 3 appeared separated by ca. 0.6 ppm (vide infra). In the UV spectra, 2 with a dienone structure shows the absorption maxima at the longer wavelengths compared to 3 with a quinone structure.[8]

From the synthetic viewpoint of thiazolo-1,2,4-triazinones, the presently available synthetic methods show drawbacks in their moderate or low yield,[9] limited availability of the starting materials[5,10] and low selectivity.[11] In

Table I. The Selective Cyclization of 3-Propargylthio-1,2,4-triazin-5(2H)-ones (1) to Thiazolo-1,2,4-triazinones 2 and/or 3

entry	1	R^1	R^2	catalyst[a] Pd[b] (mol%)	NaOH[c]	reaction condition	conversion (%)	product yield[d] (%) 2	3	4
1	1a	H	H	5	-	CH_3CN, reflux, 6 h	94	56	0	14
2	1a	H	H	-	50	CH_3OH, reflux, 4 h	59	0	76	0
3	1b	Me	H	2	-	DME, reflux, 2 h	100	64	26	4
4	1b	Me	H	-	20	CH_3OH, reflux, 4 h	68	0	74	0
5	1c	Ph	H	5	-	DME, reflux, 6 h	100	43	8	25
6	1c	Ph	H	-	10	CH_3OH, reflux, 9 h	62	23	73	0
7	1d	Me	Me	2	-	CH_3OH, reflux, 2 h	100	70	10	5
8	1d	Me	Me	-	10	CH_3OH, reflux, 4.5 h	88	0	87[e]	0
9	1e	Ph	Me	2	-	DME, reflux, 2 h	100	70	15	3

a) The effects of the amount of catalysts on reactions were not examined thoroughly. b) $PdCl_2(PhCN)_2$ was used. c) Indicated amounts of 1 N NaOH was added to the 10^{-1}M reaction solution. d) Yield refers to the isolated one based on conversion. e) The product is a mixture of 2,6-dimethyl-3-methylene-2,3-dihydro-7H-thiazolo[3,2-b][1,2,4]triazin-7-one (3d) and 2,3,6-trimethyl-7H-thiazolo[3,2-b][1,2,4]triazin-7-one (52 : 48).[12]

comparison with these, the efficiency of the present method is apparent because 2 and 3 can each be selectively prepared by the selection of reaction conditions using 1 as a sole starting material. The efficiency of the present method may also be augmented by the ease with which it is performed as typified in the following examples.

(a) Pd(II)-catalyzed reaction: An CH_3CN (10 ml) solution of 1a (1 mmol) and $PdCl_2(PhCN)_2$ (0.05 mmol) is refluxed for 6 h under nitrogen atmosphere. After evaporation of the solvent, the residue is directly subjected to a column purification (silica gel, $CHCl_3$ - CH_3OH gradient) to provide spectroscopically pure 2a (56% yield based on 94% conversion). 2a: mp 134.1 °C (dec., EtOH); m/e 167 (M^+) ; IR (nujol) 1690 (s), 1525 (m), 1330 (m), 1210 (m) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 4.07 (t, J = 1.8 Hz, 2 H), 5.32 (q, J = 1.8 Hz, 1 H), 6.57 (q, J = 1.8 Hz, 1 H), 8.19 (s, 1 H).

(b) NaOH catalyzed reaction: A mixture of 1a (1 mmol) and 1 N NaOH (0.5 mmol) in 10 ml of CH_3OH is refluxed for 4 h. The solvent was removed under reduced pressure and the residue is directly subjected to a column chromatography to give pure 3a (76% yield based on 59% conversion) 3a: mp 160-163 °C (n- hexane - acetone); m/e 167 (M^+) ; IR (nujol) 1645 (s), 1560 (m), 1305 (m) cm^{-1} ; ^1H NMR ($CDCl_3$) δ 4.19 (t, J = 2.1 Hz, 2 H), 4.89 (q, J = 2.1 Hz, 1 H), 5.52 (q, J = 2.1 Hz, 1 H), 7.61 (s, 1 H).

References and Notes

1 Hegedus, L. S.; Winton, P. M.; Varaprath, S. J. Org. Chem. 1981, 46, 2215. Some other examples are listed therein.

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3 Treatment of 1b in refluxing CH_3OH resulted in its complete recovery.

4 Alkylation of 3-methylthio-6-alkyl-1,2,4-triazin-5(2H)-ones with CH_3I in the presence of base provides only N-2 alkylation product, while in the case of 6-phenyl derivative a mixture of N-2 and N-4 alkylation product is obtained in a 4:1 ratio. (a) Gut, J.; Prystaš, M.; Jonáš, J. Collect. Czech, Chem. Commun. 1961, 26, 986. (b) Daunis, J.; Guindo, Y.; Jacquier, R.; Viallefont, P. Bull. Soc. Chim. Fr. 1972, 1511.

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8 See Reference 4b. e.g. 2b: λ_{max}^{EtOH} 305 nm (ϵ = 2,100), 231 nm (ϵ = 2,400); 3b: λ_{max}^{EtOH} 257 nm (ϵ = 18,500)

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10 For the synthesis of the type of compound 2, to our knowlege, there is only one method, which consists of a condensation of 2-hydrazinothiazoles with α-ketoacids. (a) Doleschall, G.; Lempert, K. Acta Chim. Acad. Sci. Hung. 1967, 53, 397. (b) Le Count, D. J.; Taylor, P. J. Tetrahedron 1975, 31, 433.

11 Nyitrai, J.; Bekassy, S.; Lempert, K. Acta Chim. Acad. Sci. Hung. 1967, 53, 309. 3-Methyl-6,7-dihydro-4H-thiazolo[2,3-c][1,2,4]triazin-4-one and 6-methyl-2,3-dihydro-7H-thiazolo[3,2-b][1,2,4]triazin-7-one are obtained in a ratio 4:6 by the reaction of 3-thio-6-methyl-1,2,4-triazine-3,5(2H, 4H)-dione and 1,2-dibromoethane.

12 The isolated 3d was isomerized to 2,3,6-trimethyl-7H-thiazolo[3,2-b]-[1,2,4]triazin-7-one in 90% yield (0.1 equiv of NaOH in refluxing CH_3OH for 1 h).

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