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SYNTHESIS OF 9-ARYL-6,6-DIMETHYL-5,6,7,9-TETRAHYDRO-1,2,4-TRIAZOLO-[5,1-*b*]QUINAZOLIN-8(4H)ONES

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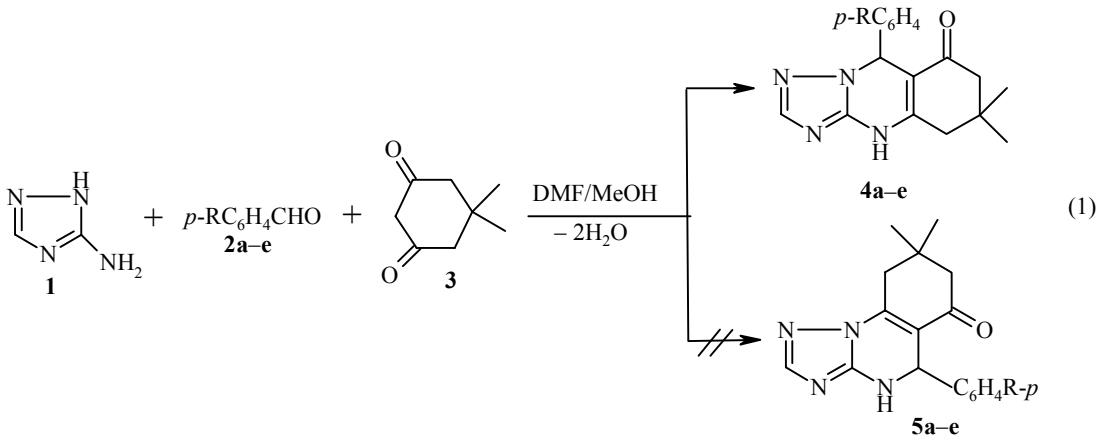
The reaction of 3-amino-1,2,4-triazole with arylidene derivatives of dimedone and their potential synthetic equivalents leading to the formation of 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydro-1,2,4-triazolo-[5,1-b]quinazolin-8(4H)ones has been studied. The direction of heterocyclization has been established, and the possible mechanisms for the formation of the pyrimidine heterocycle have been analysed.

Keywords: 3-amino-1,2,4-triazole, arylidene derivatives of dimedone, partially hydrogenated quinazoline systems, cyclocondensation.

Condensed heterocyclic systems with a partially or completely reduced pyrimidine ring are of interest since they include valuable pharmacological substances: effective coronary vasodilators [1,2] and calcium channel antagonists [3,4].

We have examined the possibility of obtaining di- and tetrahydroazolopyrimidines based on the interaction of α-amino azoles with α,β-unsaturated ketones, Mannich bases hydrochlorides, arylidene derivatives of Meldrum's acid, and esters of substituted cinnamic acids [5-8]. In attempting to broaden the reagents used in the synthesis of partially hydrogenated azolopyrimidines, in this work we have studied the condensation of 3-amino-1,2,4-triazole (**1**) with *p*-substituted benzaldehydes **2a-e** and 5,5-dimethylcyclohexane-1,3-dione (dimedone **3**) under a variety of conditions.



(1)

2, 4, 5 a R = H, **b** R = MeO, **c** R = NMe_2, **d** R = Cl, **e** R = NO_2

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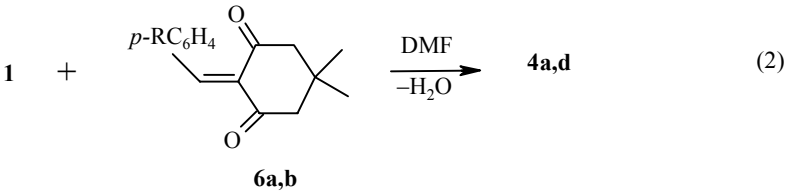
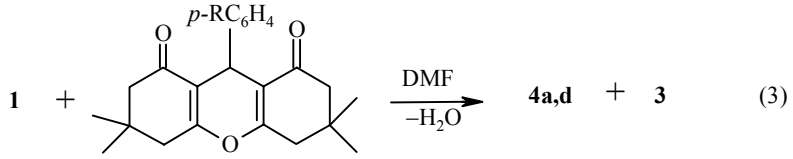


6a,b



7a,b

6, **7** **a** R = H, **b** R = Cl

The corresponding 9-aryl-6,6-dimethyl-5,6,7,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4H)-ones **4a-e** were obtained as a result of refluxing equimolar amounts of amine **1**, a substituted benzaldehyde **2a-c**, and dimedone **3** in DMF or methanol. Analogous results were obtained from condensations between amine **1** and arylidene derivatives of dimedone **6a,b** or the xanthenediones **7a,b**. In the latter case the formation of compounds **4a,d** was accompanied by the loss of a molecule of dimedone **3**.

The structure of compounds **4a-e** was confirmed by infrared (Table 1), ^{1}H NMR (Table 2), and mass spectrometry. Peaks of the molecular ions at *m/z* 294 and 329 respectively were recorded in the mass spectra of compounds **4a** and **4d**. The infrared spectra of all of the products **4a-d** were all of a type: an intense carbonyl absorption band was observed at 1652-1644 and a broad band was found in the range from 3350 to 2650 cm^{-1} which is the result of superposition of associated NH groups, methyl, and methylene groups.

The formation of isomeric tricyclic systems **4a-e** and **5a-e** is possible in these reactions. Analysis of the ^{1}H NMR spectra provided answers on the regioselectivity of the cyclocondensation. There are signals for the protons of the aromatic ring, singlets for the CH_3 group, AB systems of the two methylene groups, singlets for the methyne protons of the triazole and dihydropyrimidine rings, and the broad singlet for the imino groups (Table 2). We have previously, on the basis of related compounds (dihydroazolopyrimidines, annelated carbocycles), revealed the existence of a relationship between the position of the signal for the NH proton and the nature of the dihydropyrimidine fragment. In the spectra of analogs of compounds **4** – 5,6,7,9-tetrahydro-4H-1,2,4-triazolo[5,1-*b*]quinazolines – it was observed in the 9.5-10.5 ppm region (in DMSO-d_6), whereas in isomeric structures of type **5** it appeared at considerably higher field (by 2-3 ppm) [9, 10]. The position of the signal of the NH proton in the products synthesized (11.1-11.3 ppm) is in complete agreement with the structures **4a-e**; their additional low field shift is due to the electron-acceptor effect of the conjugated carbonyl groups.

The structures of these compounds correspond to the direction of the interaction established earlier in the reactions between amine **1** and arylidencycloalkanones [9, 11]. Formation of the pyrimidine ring with participation of the arylidene derivatives **6a,b** occurs *via* interaction of the β-carbon atom of the enone with the endocyclic atom of the aminoazole, and the carbonyl group with the amino group.

Dimedone is capable of interacting with benzaldehydes to give both the arylidene derivatives **6** and the xanthenediones **7** [12, 13]. For compound **7** in its turn it is necessary to exclude the possibility or retrocondensation. Hence, taking into account the identity of the products of reactions (1) - (3), it should be proposed that these processes are not independent but occur *via* the initial formation of the unsaturated diketones **6**. In fact investigation of the composition of the reaction mixture during the reaction of benzaldehyde **2a** with dimedone **3** in DMF by TLC established the simultaneous presence of the arylidene derivative **6a** and

TABLE 1. Characteristics of Compounds **4a-e** and **8**

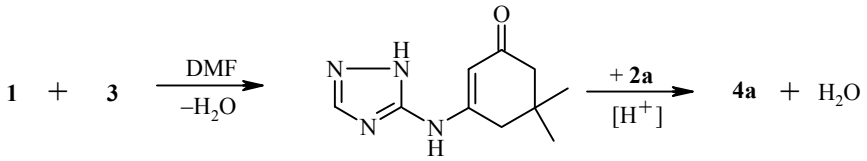
Compound	Empirical formula	Found N, % / Calculated N, %	mp, °C	IR spectrum (KBr), ν, cm^{-1}	Yield, %
4a	$C_{17}H_{18}N_4O$	19.2 / 19.1	248-250	350-2600, 1648, 1576	76 (A), 71 (B), 48 (C)
4b	$C_{18}H_{20}N_4O_2$	17.5 / 17.3	222-224	3300-2600, 1652, 1576	62
4c	$C_{19}H_{23}N_5O$	21.0 / 20.8	286-288	3350-2600, 1648, 1580	72
4d	$C_{17}H_{17}ClN_4O$	17.1 / 17.0	281-283	3350-2650, 1648, 1556	65 (A), 62 (B), 60 (C)
4e	$C_{17}H_{17}N_5O_3$	19.9 / 20.7	284-285	3350-2650, 1644, 1576	59
8	$C_{10}H_{14}N_4O$	27.0 / 27.2	285-287	3300-2500, 1580, 1540	51

the xanthenedione **7a**. At the same time prolonged refluxing of compound **7a** in DMF did not lead to the appearance in solution of any new substances. These results confirm that the reaction between amine **1** and xanthenediones **7a,b** occur by an independent route and not *via* initial destruction of the xanthenediones to the arylidene derivatives **6** and dimedone **3**.

Evidently in reaction (3) in the first stage attack occurs on the side of the exocyclic amino group of the aminotriazole by one of the electrophilic centers in α-position to the bridge oxygen atom in compounds **7**. As a result opening of the pyrane ring occurs with elimination of a molecule of dimedone. The process of formation of the dihydropyrimidine ring is completed by interaction of the imino group of the imino azole with the β-carbon of the electrophilic center to give a product with structure **4**.

It is probable that both mechanisms occur in reaction (1) because both the arylidene derivative and the xanthenediones are present simultaneously in the reaction mixture. At the same time the route connected with initial formation of an enamino ketone by reaction of the carbon atom of the carbonyl in dimedone **3** with the amino group of amine **1**, similar to the reaction of dimedone **3** with aromatic amines [14], is not excluded.

To test the possibility that reaction (1) occurs *via* preliminary reaction of the aminotriazole **1** with diketone **3** and the aldehydes **2a-e**, we investigated the condensation of diketone **3** with the aminotriazole **1**. It appeared that, when equimolar amounts of the starting materials were refluxed in DMF, compound **8** was formed, whose structure was established methods (Table 1). According to mass-spectroscopic data $M^+ = 206$ for compound **8**. Consequently, a molecule of water is lost when the amine reacts with the diketone. In the ^1H NMR spectrum of **8** (see Experimental), the presence of singlets for two NH groups and a methyne proton of an enone fragment are in complete agreement with the proposed structure of **8**.



8

To determine the possibility of cyclocondensation of the enamino ketone **8** with benzaldehyde it was refluxed with benzaldehyde **2a** in nitrobenzene, in DMF without a catalyst and in the presence of a catalytic amount of hydrochloric acid. Product **4a** was isolated only from the reaction mixture containing a catalyst. Thus the probability of formation of compound **4a** *via* preliminary formation of the enamino ketone **8** under the conditions of reaction (1) is small.

TABLE 2. ^{1}H NMR Spectra of Compounds **4a-e**

Com-pound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)						
	NH (1H, s)	2-H (1H, s)	H_{Ar}	9-CH (1H, s)	5-, 7-H_A (1H, d)*	5-, 7-H_B (1H, d)*	*gem*-$(CH_3)_2$ (3H, s and 3H, s)
4a	11.10	7.73	7.11-7.40 (5H, m)	6.20	2.50 and 2.06	2.54 and 2.15	0.90 and 1.10
4b*[2]	11.10	7.67	6.95 (4H, dd)	6.16	2.49 and 2.04	2.54 and 2.22	0.98 and 1.05
4c*[3]	11.02	7.64	6.85 (4H, dd)	6.08	2.47 and 2.06	2.54 and 2.23	0.99 and 1.05
4d	11.20	7.71	7.31 (4H, dd)	6.22	2.50 and 2.09	2.54 and 2.22	0.96 and 1.04
4e	11.31	7.74	7.85 (4H, dd)	6.38	2.50 and 2.09	2.56 and 2.23	0.96 and 1.05

* J_{AB} for compounds **4a-e** from 15.9-16.2 Hz.
*[2] A signal is also present at 3.70 ppm (3H, s, OCH_3).
*[3] A signal is also present at 2.80 ppm (6H, s, $N(CH_3)_2$.

EXPERIMENTAL

IR spectra were recorded with a Specord M-82 spectrometer, and ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were measured on a Varian 300 (300 MHz) spectrometer. Electron impact mass spectra were recorded with a Finnigan SSQ 710 spectrometer with direct introduction of the sample into the ion source. Composition of reaction mixtures and purity of the compounds obtained were monitored by TLC on Silufol UV-254 strips with 1:1 acetone–chloroform and 9:1 chloroform–methanol as eluents.

6,6-Dimethyl-9-phenyl-5,6,7,9-tetrahydro-1,2,4-triazolo[5,1-*b*]quinazolin-8(4H)-one (4a). A. A mixture of dimedone **3** (0.14 g, 1 mmol), benzaldehyde **2a** (0.11 g, 1 mmol), and amine **1** (0.08 g, 1 mmol) in DMF (1 ml) was refluxed for 30 min. 2-Propanol (5 ml) was added to the cooled reaction mass and the product **4a** (0.22 g) was filtered off and recrystallized from a 1:2 mixture of DMF and 2-propanol.

Compounds 4b-c were prepared analogously using the corresponding substituted benzaldehyde.

B. A mixture of 2-benzylidene-5,5-dimethylcyclohexane-1,3-dione (**6a**) (0.23 g, 1 mmol) [12] and amine **1** (0.08 g, 1 mmol) in DMF (1 ml) was refluxed for 30 min. 2-Propanol (5 ml) was added to the cooled reaction mass and the precipitate of product **4a** (0.21 g) was separated by filtration.

Compound 4d was prepared analogously from 2-(4-chlorophenylidene)-5,5-dimethylcyclohexane-1,3-dione (**6b**) [12].

C. A mixture of 3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydroxanthene-1,8(2H)-dione (**7a**) (0.33 g, 1 mmol) [13] and amine **1** (0.08 g, 1 mmol) DMF (1 ml) was refluxed for 30 min. The reaction mixture was worked up analogously to method B and compound **4a** (0.14 g) was isolated. The filtrate was extracted with chloroform. The extract was dried over sodium sulfate which was then filtered off, and the extract was evaporated. Dimedone **3** (0.13 g) was isolated from the oily residue with the help of methanol. Mp 150-151°C (mp 150°C [15]).

Compound 4d was prepared analogously from 3,3,6,6-tetramethyl-9-(4-chlorophenyl)-3,4,5,6,7,9-hexahydroxanthene-1,8(2H)-dione (**7b**) [13].

5,5-Dimethyl-3-(1H-1,2,4-triazol-5-ylamino)-2-cyclohexen-1-one (8). A mixture of amine **1** (0.1 g, 1 mmol) and dimedone (**3**) (0.14 g, 1 mmol) in DMF (1 ml) (or nitrobenzene) was refluxed for 90 min. The reaction mass was cooled, 2-propanol (5 ml) was added, and compound **8** (0.11 g) was filtered off and

recrystallized from a 1:2 mixture of DMF and 2-propanol. ^{1}H NMR spectrum, δ, ppm: 13.61 (1H, s, 3-NH), 9.60 (1H, s, NH in Het); 8.39 (1H, s, 3-H_{Het}); 6.44 (1H, s, 2-H); 2.05 (2H, 4- and 6-H_A); 2.54 (2H, s, 4- and 6-H_B); 1.01 (6H, s, *gem*-$(CH_3)_2$).

Cyclocondensation of 5,5-Dimethyl-3-(1H-1,2,4-triazol-5-ylamino)-2-cyclohexen-1-one (8) with Benzaldehyde. A mixture of the enamino ketone **8** (0.21 g, 1 mmol) and benzaldehyde **2a** (0.11 g, 1 mmol) in DMF (1 ml) was refluxed for 1 h in the presence of a catalytic amount of HCl. After cooling, product **4a** (0.2 g) was isolated.

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