Synthesis and heteroelectrocyclization of unsymmetrically substituted diazomalonamides ✽

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A selective procedure was developed for the synthesis of 1,2,3-triazoles and unsymmetrically substituted diazomalonamides. Cyclization of unsymmetrically substituted diazomalonamides to 1,2,3-triazoles was studied by the method of intramolecular competitive reactions. The kinetic and thermodynamic characteristics of the process were determined. Quantum-chemical calculations for the monorotatory electrocyclic and nonrotatory heteroelectrocyclic mechanisms of cyclization were carried out. *N*-Aryldiazomalonamides undergo cyclization according to the heteroelectrocyclic mechanism, whereas cyclization of *N*-alkyldiazomalonamides proceeds by the monorotatory mechanism. The experimental constant of competition between these processes is $(1.3—8.3)\cdot10^3$ (DMSO-d_6) and $(45.2—72.4)\cdot10^3$ (CD_3OD).

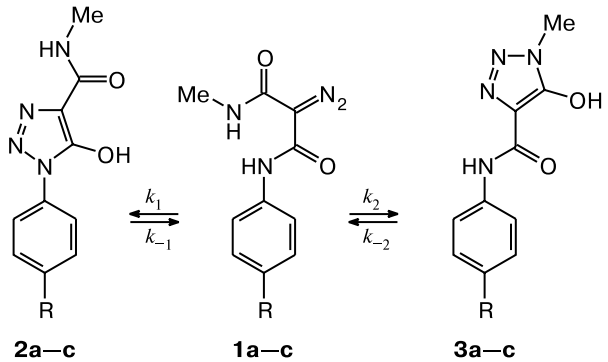
Key words: 1,2,3-triazoles, diazo compounds, method of intramolecular competitive reactions, cyclization, quantum-chemical calculations, thermodynamic stability, rate constant.

Chemistry of aliphatic diazo compounds has been extensively developed over the last several decades.[1—4] Diazoalkanes bearing the carbamoyl group in the α position are of particular interest. These compounds were used for the synthesis of 1,2,3-triazole derivatives, which have found wide application in synthetic organic chemistry, technology, and medicine.[5,6] Compounds of this class attract considerable interest because of their biological activity.[7—9] For example, the 1,2,3-triazole ring is involved as a structural fragment in many β-lactam antibiotics (for example, in Tazobactam or Cefatrizine). 1,2,3-Triazoles have also found extensive use in technology[5,10] as color-sensitive reagents, metal corrosion inhibitors, and light stabilizers for polymers.

However, cyclization pathways of unsymmetrical diazomalonamides to isomeric 5-hydroxy-1,2,3-triazoles are scantily studied. Earlier, we have demonstrated[11] that the transformation of diazoacetamides into 5-hydroxy-1,2,3-triazoles can occur by two different mechanisms, *viz.*, as either the classical electrocyclic process or the 1,5-heteroelectrocyclic process, depending on the substituent at the nitrogen atom of the carboxamide group.

In the present study, we examined regioselective cyclization of unsymmetrical diazomalonamides **1a—c** to 1,2,3-triazoles **2a—c** or **3a—c** (Scheme 1).

Scheme 1



2a—c **1a—c** **3a—c**

R = Me (**a**), OMe (**b**), Br (**c**)

$K_1 = k_{-1}/k_1 = [\mathbf{1}]/[\mathbf{2}]$, $K_2 = k_{-2}/k_2 = [\mathbf{1}]/[\mathbf{3}]$, $K = [\mathbf{3}]/[\mathbf{2}]$.

Results and Discussion

Unsymmetrical diazomalonamides were synthesized according to two methods: 1) by diazotization of 2-aminomalonamides **4a—c**, which were prepared from malonamides **5a—c** through oximes **6a—c** (Scheme 2) in a total yield of 20—45%; 2) by diazo transfer[4] to malonamides **5a—c** (Scheme 3).

The reaction of amides **5a—c** with tosyl azide generates diazo compounds **1**. Under basic conditions,[5] the latter could undergo cyclization at the alkylamide or arylamide group to give isomeric triazoles **2** or **3**. We demonstrated that under basic conditions, the arylamide group in compound **1** is more reactive than the alkylamide group. Only 1-aryl-1,2,3-triazolates **7a—c** were isolated in good yield, whereas the isomeric product was not de-

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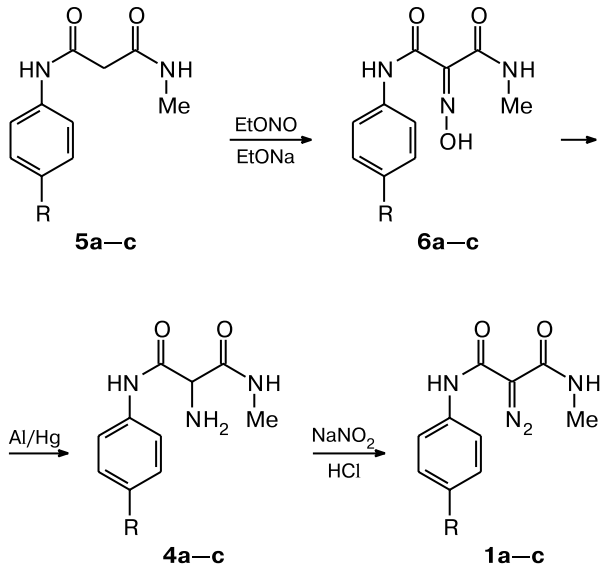
Scheme 2



R = Me (**a**), OMe (**b**), Br (**c**)

tected by TLC. The ^{1}H NMR spectra of heterocycles **7a—c** show signals of aromatic protons (and the substituent in the aromatic ring, Table 1) at δ 7.00—8.00, a one-proton quartet of the NHMe proton at δ 10.00—10.50, and a three-proton doublet of the NHMe group at δ 2.80—3.00.

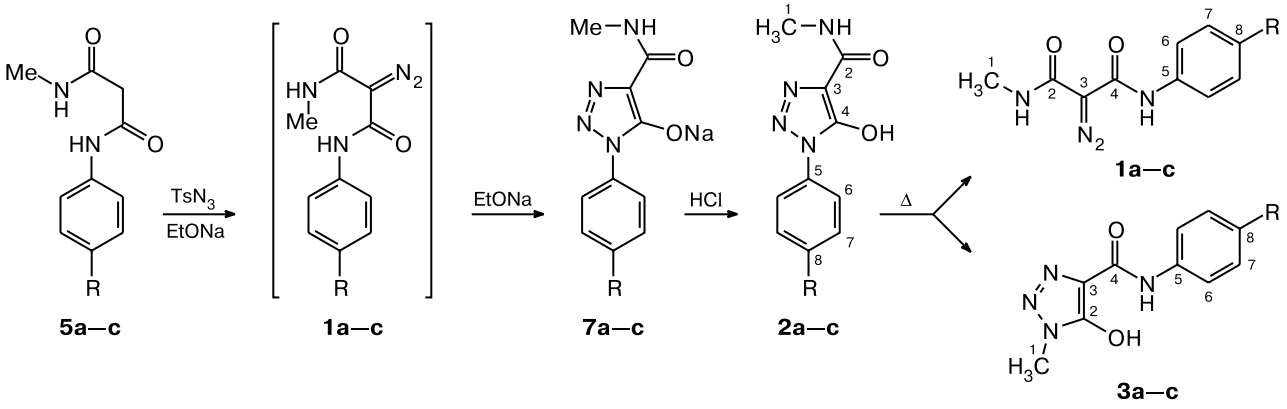
After treatment of aqueous solutions of compounds **7a—c** with concentrated hydrochloric acid, 1-aryl-1,2,3-triazoles **2a—c** were isolated in good yields. Refluxing of solutions of compounds **2a—c** in toluene for 10 h afforded 1-methyl-1,2,3-triazoles **3a—c** (in 60—80% yields) as precipitates. Diazomalonamides **1a—c** were isolated from the filtrate in 20—30% yields upon cooling. The IR spectra of diazo compounds **1a—c** have a characteristic absorption band[12,13] of the diazo group at 2250 cm^{-1}. The characteristics of these compounds are identical to those of compounds prepared by diazotization of 2-aminomalonamides **4a—c**. Therefore, we developed a new regioselective procedure for the synthesis of isomeric 1-aryl-1,2,3-triazoles **2**, 1-alkyl-1,2,3-triazoles **3**, and unsymmetrically substituted diazomalonamides **1** by the Cornforth rearrangement.

Table 1. ^{1}H NMR spectra (DMSO-d$_6$) of compounds **1a—c**, **2a—c**, and **3a—c**

Compound	δ			
	Me	ArH (d)	R (s)	NH
1a	2.82 (d)	7.66, 7.38	2.26	9.80 (s), 10.40 (q)
1b	3.09 (d)	7.76, 7.00	3.92	9.90 (s), 10.40 (q)
1c	2.77 (d)	7.53, 7.48	—	8.60 (q)
2a	2.77 (d)	7.40, 7.12	2.26	10.50 (q)
2b	3.02 (d)	7.78, 7.05	3.82	10.60 (q)
2c	2.83 (br.s)	7.81, 7.77	—	8.36 (br.s)
3a	3.72 (s)	7.61, 7.11	2.38	9.82 (s)
3b	3.78 (s)	7.75, 7.05	3.96	9.80 (s)
3c	3.74 (s)	7.77, 7.50	—	10.24 (s)

The kinetics and the equilibrium for the rearrangement of 1-aryl-1,2,3-triazoles **2a—c** into diazomalonamides **1a—c** and 1-methyl-1,2,3-triazoles **3a—c** were studied by ^{1}H NMR spectroscopy in CD_3OD and DMSO-d$_6$ at 50 °C. We demonstrated (Table 3) that the ternary equilibrium is shifted toward 1-alkyl-1,2,3-triazoles **3a—c**. The use of CD_3OD instead of DMSO as the solvent leads to better stabilization of diazo compound **1** (see Table 3). Based on the results of our study, compounds **1—3** can be arranged in the order of decreasing thermodynamic stability as follows: 1-methyl-1,2,3-triazoles **3** > diazomalonamides **1** > 1-aryl-1,2,3-triazoles **2**.

Scheme 3



R = Me (**a**), OMe (**b**), Br (**c**)

Table 2. ^{13}C NMR spectra (DMSO-d_6) of compounds **1a—c**, **2a—c**, and **3a—c**

Compound	δ					
	C(1)	C(2)	C(3)	C(4)	C(5), C(6), C(7), C(8)	R
1a	26.1	162.6	64.8	160.3	137.90, 135.75, 129.26, 119.55	20.4
1b	26.9	162.3	65.0	160.8	139.9, 130.7, 125.2, 121.5	55.0
1c	26.1	162.4	65.3	160.4	137.6, 131.4, 121.5, 114.9	—
2a	25.2	160.3	105.2	153.2	138.03, 132.69, 129.73, 122.00	20.6
2b	26.0	160.1	110.1	154.0	138.0, 132.9, 129.7, 122.0	56.0
2c	25.2	162.4	115.2	153.0	134.5, 132.2, 123.4, 120.8	—
3a	31.8	156.7	116.5	162.3	133.81, 132.20, 130.62, 129.60	20.8
3b	31.9	159.9	115.2	161.3	137.8, 132.0, 129.6, 120.6	55.2
3c	31.7	152.2	114.9	158.8	138.1, 131.6, 121.7, 115.3	—

Table 3. Ternary equilibrium of diazomalonamides **1a—c** and triazoles **2a—c** and **3a—c** in DMSO-d_6 and CD_3OD (in parentheses)

Compound	Content (%)			Equilibrium constants		
	1	**2**	**3**	K_1	K_2	K
a	6.6 (10.9)	4.1 (1.5)	89.3 (87.6)	1.610 (7.267)	0.07391 (0.1244)	21.78 (58.40)
b	6.0 (9.8)	5.4 (1.6)	88.6 (88.6)	1.111 (6.125)	0.06772 (0.1106)	16.41 (55.38)
c	11.0 (13.8)	4.3 (0.8)	84.7 (85.4)	2.558 (17.25)	0.1299 (0.1616)	19.70 (106.8)

The typical kinetic curves for the rearrangements under study are shown in Fig. 1. It should be noted that the concentration of diazo compounds **1a—c** changes only slightly in the course of the process. However, the observed constant of formation of 1-methyl-1,2,3-triazoles **3a—c** is substantially smaller than the constant of disappearance of 1-aryl-1,2,3-triazoles **2a—c** (Table 4). Therefore, the kinetic equations can be reduced to Eqs (1) and (2) using the stationary state method.[14]

$$dA/dt = -\frac{k_1k_{-2} + k_{-1}k_2 + k_{-1}k_{-2}}{k_1 + k_{-2} + k_2}(A - A_\infty) \quad (1)$$

$$dC/dt = -\frac{k_1k_{-2} + k_{-1}k_2 + k_{-1}k_{-2}}{k_1 + k_{-2} + k_{-1}}(C_\infty - C) \quad (2)$$

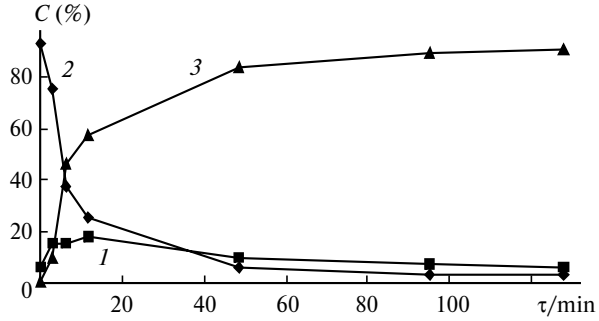


Fig. 1. Concentration dependence of compounds **1a** (*1*), **2a** (*2*), and **3a** (*3*) on the reaction time in CD_3OD.

The rate constants k_1, k_2, k_{-1}, and k_{-2} (see Scheme 1) can be calculated from the equilibrium constants K_1, K_2, and K according to Eqs (3)—(6) (Table 5). These equations were derived analogously to those reported earlier.[11]

$$k_1 = \frac{k_{dis}k_{-2}}{k_{app}(1 + K_1 - k_{dis}/k_{app})} \quad (3)$$

$$k_{-2} \approx k_{dis}/(1 + K + K_1) \quad (4)$$

$$k_2 = k_{-2}/K_2 \quad (5)$$

$$k_{-1} = k_1K_1 \quad (6)$$

Therefore, we demonstrated that cyclization of the diazo group at the arylamide group occurs much more

Table 4. Observed constants of disappearance (k_{dis}) of 1-aryl-1,2,3-triazoles **2a—c** and constants of appearance (k_{app}) of 1-alkyl-1,2,3-triazoles **3a—c** in DMSO-d_6 and CD_3OD

Compound	k_{dis} (**2a—c**)				k_{app} (**3a—c**)			
	DMSO-d_6		CD_3OD		DMSO-d_6		CD_3OD	
	$k_{dis} \cdot 10^6/s^{-1}$	r^2	$k_{dis} \cdot 10^7/s^{-1}$	r^2	$k_{app} \cdot 10^7/s^{-1}$	r^2	$k_{app} \cdot 10^7/s^{-1}$	r^2
a	22.30±0.05	0.9992	56.61±0.04	0.9993	85.45±0.05	0.9989	6.848±0.008	0.9994
b	18.98±0.08	0.9989	65.40±0.05	0.9991	89.91±0.07	0.9991	9.179±0.005	0.9991
c	25.33±0.07	0.9987	112.0±0.6	0.9994	71.19±0.09	0.990	6.137±0.005	0.9992

Table 5. Calculated constants of cyclization of unsymmetrically substituted diazomalonamides **1a—c** to triazoles **2a—c** and **3a—c**

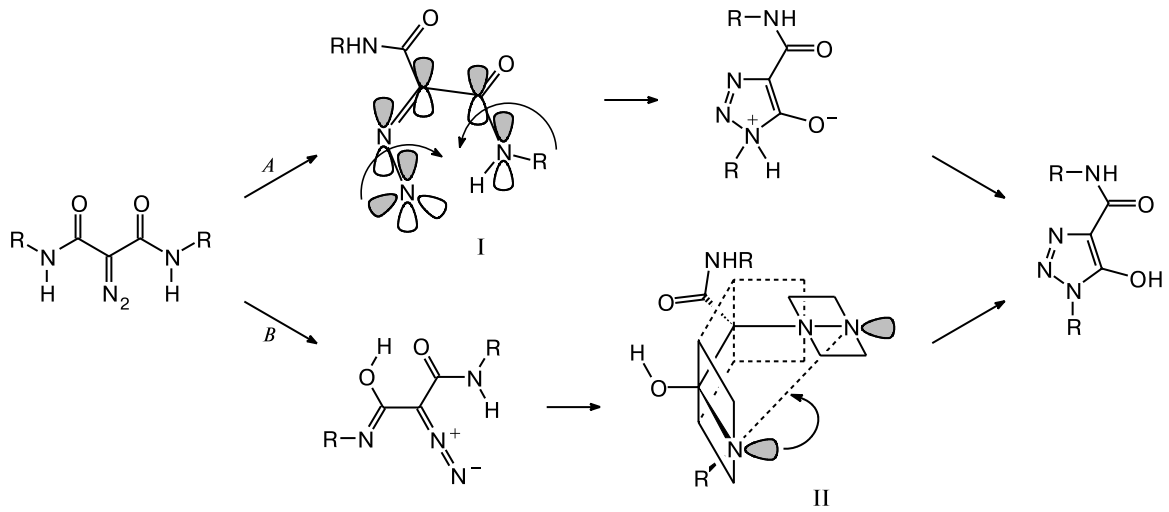
Compounds **1—3**	DMSO-d_6					CD_3OD				
	$k_1 \cdot 10^2$	$k_{-1} \cdot 10^2$	$k_2 \cdot 10^6$	$k_{-2} \cdot 10^6$	k_1/k_2	$k_1 \cdot 10^2$	$k_{-1} \cdot 10^2$	$k_2 \cdot 10^7$	$k_{-2} \cdot 10^7$	k_1/k_2
	s^{-1}					s^{-1}				
a	5.57	8.97	12.4	0.914	4500	3.61	26.2	6.82	0.849	52800
b	1.95	2.16	15.1	1.02	1290	1.82	11.2	9.46	1.05	19300
c	6.98	17.9	8.39	1.09	8320	4.01	69.2	5.54	0.896	72400

rapidly than that at the alkylamide group. The constant of competition between these processes is $(1.3—72.4) \cdot 10^3$ (see Table 5). The difference in the activation energy is 4.6—7.3 kcal mol^{-1}.

We carried out semiempirical quantum-chemical calculations (PM3 method)[15—17] and the density functional theory (DFT) at the BLYP/6-31G(d) level[18] for the electrocyclic (I) and heteroelectrocyclic (II) (Scheme 4) mechanisms of cyclization of diazomalonamides. The activation energy for the electrocyclic (with rotation about the terminal nitrogen atoms) mechanism of cyclization of both *N*-aryl- and *N*-alkylamides (see Scheme 4, path *A*) is 32—34 (BLYP/6-31G(d)) and 36—41 kcal mol^{-1} (PM3) (the rate constant is $3 \cdot 10^{-9}—1 \cdot 10^{-14}$ s^{-1}). The activation energy for the heteroelectrocyclic mechanism (no rotation about the terminal bonds occurs, and a new σ-bond is formed with the involvement of the lone electron pair and the unoccupied orbital located orthogonal to the π system in the plane of the molecule[19—26]) of cyclization of diazomalonamides is 18—22 (BLYP/6-31G(d)) and 22—24 (PM3) kcal mol^{-1} (the rate constant is $1.2 \cdot 10^{-2}—5 \cdot 10^{-4}$ s^{-1}). These values agree well with the experimental rate constants k_1 and k_2 determined in the study of the equilibrium (see Table 5). It should be noted that the calculations for the gas phase by both the PM3 and DFT methods showed no difference for the alkyl and aryl derivatives. In both cases, the heteroelectrocyclic mechanism is preferable to the electrocyclic one.

Substituents in the aryl residue have different effects on cyclization of the diazo group at the nitrogen atom of the carbamoyl group containing an aromatic or alkyl substituent. Electron-withdrawing substituents accelerate cyclization at the anilide nitrogen atom and, on the contrary, decelerate cyclization at the nitrogen atom of the methylcarbamoyl group (see Table 5). This is attributable to the fact that in the case of the electrocyclic mechanism, where a new σ bond is formed with the involvement of orbitals of the π system, a decrease in the electron density in the π system due to the presence of π-conjugated electronegative substituents hinders cyclization. In the case of the heteroelectrocyclic mechanism, where a new σ bond is formed due to interactions of orbitals located perpendicular to the π system, this conjugation facilitates the electron density redistribution in the π system, which has no effect on the cyclization process (the π system is not involved in the formation of a σ bond) and only contributes to stabilization of the transition aromatic

Scheme 4



state, thus decreasing the activation energy of cyclization proceeding by the heteroelectrocyclic mechanism. If the lone electron pair of the nitrogen atom of the carbamoyl group is involved in π conjugation, electron-withdrawing substituents will decelerate cyclization. If the carbamoyl group is in the tautomeric oxyimine form, the lone electron pair of the nitrogen atom is orthogonal to the π system and the electron-withdrawing substituents promote the reaction.

It can be concluded that cyclization of unsymmetrically substituted diazomalonamides also proceeds by two different mechanisms, *viz.*, by the pseudopericyclic mechanism for aryl derivatives and the monorotatory mechanism for alkyl derivatives. This provides an explanation for the fact that only one isomer is formed in the diazo transfer to malonamides **5a—c**. Since the rate of cyclization of the diazo group at the carboxamide fragment containing the aryl substituent is higher than that at the fragment containing the alkyl substituent, only 1-aryl-1,2,3-triazol-5-olate **2** is produced. The formation of triazol-5-olates proceeds irreversibly and, consequently, isomeric 1-alkyl-1,2,3-triazol-5-olate is not generated.

To summarize, we have developed a new selective procedure for the synthesis of diazomalonamides and 1,2,3-triazoles. The kinetic data for cyclization of diazomalonamides to isomeric 1,2,3-triazoles are consistent with the electrocyclic mechanism for cyclization of *N*-alkyldiazomalonamides and the heteroelectrocyclic mechanism for cyclization of *N*-aryldiazomalonamides.

Experimental

The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker AMX 400 instrument in DMSO-d_6 or CD_3OD with Me_4Si as the internal standard. The electron-impact mass spectra were obtained on a Varian MAT 311A instrument (40—200 °C, 70 eV). The IR spectra were measured on a UR-25 spectrometer in KBr pellets. The course of the reactions and the purity of the compounds synthesized were monitored by TLC on Silufol UV-254 plates in chloroform and the ethyl acetate—hexane (3 : 1), chloroform—ethanol (9 : 1), and chloroform—ethanol—ammonia (25%) (60 : 11 : 1) systems. All solvents were purified before use according to standard procedures.

Kinetics and equilibrium. A 0.11 *M* solution of compounds **2a—c** in DMSO-d_6 or CD_3OD was placed in an NMR tube and the tube was heated in a thermostat at 60 °C. The NMR spectrum was recorded at equal intervals. The concentration of the compounds was monitored by the integral intensity of the signals for the protons of the aromatic ring and the methyl group. The observed rate constant of the reaction was calculated using the linear regression programs.

N*-Aryl-*N*′-methyl-2-diazomalonamides (1a—c).** ***A. A solution of sodium nitrite (0.345 g, 5 mmol) in water (10 mL) was added dropwise with stirring to a solution of 2-amino-*N*-aryl-*N*′-methylmalonamide **4a—c** (5 mmol) in 1 *M* HCl (40 mL) at 0 °C. The reaction mixture was stirred for 20 min. The precipitate that formed was filtered off and dried over P_2O_5 *in vacuo*.

B. A solution of triazole **2a—c** (10 mmol) in toluene (50 mL) was refluxed for 10 h and then cooled. Triazole **3a—c** was filtered off. The filtrate was concentrated *in vacuo* and the residue containing malonamide **1a—c** was triturated in hexane.

1-Aryl-5-hydroxy-*N*-methyl-1,2,3-triazole-4-carboxamides (2a—c). Sodium 1-aryl-4-(*N*-methylcarbamoyl)-1,2,3-triazol-5-olate (**7**) (10 mmol) was dissolved in water (10 mL) and the solution was acidified with concentrated hydrochloric acid to pH 3—4 at 0—10 °C. The precipitate that formed was filtered off and dried over P_2O_5 *in vacuo*.

***N*-Aryl-5-hydroxy-1-methyl-1,2,3-triazole-4-carboxamides (3a—c).** A solution of triazole **2a—c** (10 mmol) in toluene (50 mL) was refluxed for 10 h and then cooled. Triazole **3a—c** was filtered off, dried over P_2O_5 *in vacuo*, and crystallized from ethanol.

Table 6. Characteristics of compounds **1—4**, **6**, and **7**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Molecular formula
1a	86[a], 12[b]	80 (decomp.)	57.0 / 56.89	5.4 / 5.21	24.0 / 24.12	$C_{11}H_{12}N_4O_2$
1b	90[a], 8[b]	75 (decomp.)	53.6 / 53.22	5.0 / 4.87	22.3 / 22.57	$C_{11}H_{12}N_4O_3$
1c	75[a], 10[b]	94 (decomp.)	40.5 / 40.43	3.2 / 3.05	19.0 / 18.86	$C_{10}H_9BrN_4O_2$
2a	95	126	57.0 / 56.89	5.1 / 5.21	24.1 / 24.12	$C_{11}H_{12}N_4O_2$
2b	93	135	53.3 / 53.22	4.9 / 4.87	22.6 / 22.57	$C_{11}H_{12}N_4O_3$
2c	98	186	40.5 / 40.43	2.9 / 3.05	18.9 / 18.86	$C_{10}H_9BrN_4O_2$
3a	72	139	56.6 / 56.89	5.5 / 5.21	24.2 / 24.12	$C_{11}H_{12}N_4O_2$
3b	62	156	53.2 / 53.22	5.0 / 4.87	22.7 / 22.57	$C_{11}H_{12}N_4O_3$
3c	80	189	40.5 / 40.43	3.1 / 3.05	18.9 / 18.86	$C_{10}H_9BrN_4O_2$
4a	45	96	60.0 / 59.71	7.0 / 6.83	19.2 / 18.99	$C_{11}H_{15}N_3O_2$
4b	59	68	55.5 / 55.69	6.4 / 6.37	17.8 / 17.71	$C_{11}H_{15}N_3O_3$
4c	36	115	41.5 / 41.98	4.5 / 4.23	14.9 / 14.69	$C_{10}H_{12}BrN_3O_2$
6a	64	196	56.2 / 56.16	5.4 / 5.57	17.9 / 17.86	$C_{11}H_{13}N_3O_3$
6b	59	205	52.5 / 52.59	5.5 / 5.22	16.5 / 16.72	$C_{11}H_{13}N_3O_4$
6c	65	215	39.8 / 40.02	3.8 / 3.36	13.9 / 14.00	$C_{10}H_{10}BrN_3O_3$
7a	87	>250	48.6 / 48.53	4.6 / 4.81	20.6 / 20.58	$C_{11}H_{11}N_4NaO_2 \cdot H_2O$
7b	82	>250	45.3 / 45.84	4.6 / 4.55	19.3 / 19.44	$C_{11}H_{11}N_4NaO_3 \cdot H_2O$
7c	78	>250	35.3 / 35.63	3.4 / 2.99	16.3 / 16.62	$C_{10}H_8BrN_4NaO_2 \cdot H_2O$

[a] Method *A*.
[b] Method *B*.

2-Amino-*N*-aryl-*N*´-methylmalonamides (4a—c). *N*-Aryl-2-hydroxyimino-*N*´-methylmalonamide **6** (10 mmol) was added to a suspension of aluminum amalgam (0.4 g, 1.48 mmol) in diethyl ether (50 mL) at 0 °C. The reaction mixture was stirred at 0—5 °C for 2 h. Then water (10 mL) was added. The mixture was stirred for 30 min and then filtered. Amine **4** was extracted from the precipitate with hot ethanol (3×50 mL). The combined extracts were concentrated to dryness. The residue was triturated and crystallized from ethanol.

***N*-Aryl-2-hydroxyimino-*N*´-methylmalonamides (6a—c).** Ethyl nitrite (0.83 mL, 0.75 g, 10 mmol) was added in one portion to a suspension of malonamide **5a—c** (5 mmol) in sodium ethoxide, which was prepared from anhydrous ethanol (50 mL) and sodium (0.115 g, 5 mmol), at 0—5 °C. The reaction mixture was stirred at this temperature for 2 h and concentrated *in vacuo* to dryness. Water (50 mL) was added to the residue. Unconsumed malonamide **5** was filtered off and the filtrate was acidified to pH 3. The precipitate was filtered off and crystallized from ethanol.

Sodium 1-aryl-4-(*N*-methylcarbamoyl)-1,2,3-triazol-5-olates (7a—c). A solution of tosyl azide (3.94 g, 20 mol) in ethanol (5 mL) was added dropwise to a suspension of malonamide **4a—c** (20 mmol) in sodium ethoxide, which was prepared from anhydrous ethanol (100 mL) and sodium (0.460 g, 20 mmol), at 0 °C. The reaction mixture was stirred at 0—5 °C for 2 h and concentrated *in vacuo* to dryness. The residue was suspended in water (50 mL). The precipitate containing tosylamide was filtered off and the filtrate was concentrated to dryness. The product was dried over P_2O_5 *in vacuo*.

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