Chemistry of Heterocyclic Compounds, Vol. 40, No. 7, 2004

REACTIONS OF 2-AMINO-4-METHYL-6-(2-PYRIDYL)- AND 2-AMINO-4-METHYL-6-PHENYL-7,8-DIHYDROINDAZOLO-[4,5-*d*]THIAZOLES WITH ALDEHYDES

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The reaction of 2-amino-4-methyl-6-(2-pyridyl)-7,8-dihydroindazolo[4,5-d]thiazole, obtained by treating 3-methyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole with pyridinium bromide perbromide and then with thiourea, and 2-amino-4-methyl-6-phenyl-7,8-dihydroindazolo[4,5-d]thiazole with 4-bromo-, 4-fluoro-, 4-dimethylamino-, 4-methoxy-, 3,4-dimethoxy-, and 3,4-methylenedioxy-benzaldehydes, furfural, pyridinecarbaldehyde, and thiophenecarbaldehyde gave the corresponding Schiff bases. The products of the condensation of these aminothiazoles with cinnamaldehyde, 1-(2-pyridyl)- and 4-chloro-1-(2,4-difluorophenyl)-5-formyl-3-methyl-6,7-dihydroindazoles, 2-formyl-dimedone, and 2-formyl-1,3-indanedione were also obtained.

Keywords: 2-amino-4-methyl-6-(2-pyridyl)- and 2-amino-4-methyl-6-phenyl-7,8-dihydroindazolo-[4,5-*d*]thiazoles, aromatic aldehydes, 2-formyl-1,3-cyclanediones, Schiff bases.

According to our previous work [1], we synthesized 2-amino-4-methyl-6-(2-pyridyl)-7,8-dihydroindazolo[4,5-*d*]thiazole (**3a**) by means of the bromination of 3-methyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole (**1a**) using pyridinium bromide perbromide followed by the reaction of the 5-bromo derivative obtained (**2a**) with thiourea.

Indazoles and benzthiazoles with hydrogenated carbocyclic systems as well as tricyclic condensed systems containing a hydrogenated indazole or benzthiazole fragment have recently been the subject of extensive study due to their biological activity [3-6]. In order to modify aminothiazoles **3**, we carried out condensation with various types of aldehydes, including substituted benzaldehydes, pyridinecarbaldehyde, thiophenecarbaldehyde, furfural, and cinnamaldehyde. We also carried out condensation with 1-(2-pyridyl)- and 4-chloro-1-(2,4-difluorophenyl)-5-formyl-3-methyl-6,7-dihydroindazoles, 2-formyldimedone, and 2-formyl-1,3-indanedione.

^{1}H NMR spectroscopy shows a signal for the primary amino group in **3a** at 4.98 ppm, signals for the azomethine protons of Schiff bases **4** at 8.71-9.13 ppm, and for the azomethine proton in **5** at 9.16 ppm. The ^{1}H NMR spectra of the products of the condensation of amines **3** with 2-formyl-1,3-cyclanediones clearly show signals for protons of a *trans*-arranged aminomethylene structural fragment ($\delta_{=CH-}$ 8.42-8.52 ppm, ^3J = 12 Hz, δ_{NH} 11.36-11.39 ppm, ^3J = 12 Hz). The chemical shifts of the protons of the other structural elements of **4-6** support the proposed structures. The carbonyl stretching band for α-bromo ketone **2a** is found in the IR spectrum at 1680 cm^{-1}, while the primary amino group stretching bands for **3a** are found at 3320 and 3410 cm^{-1}.

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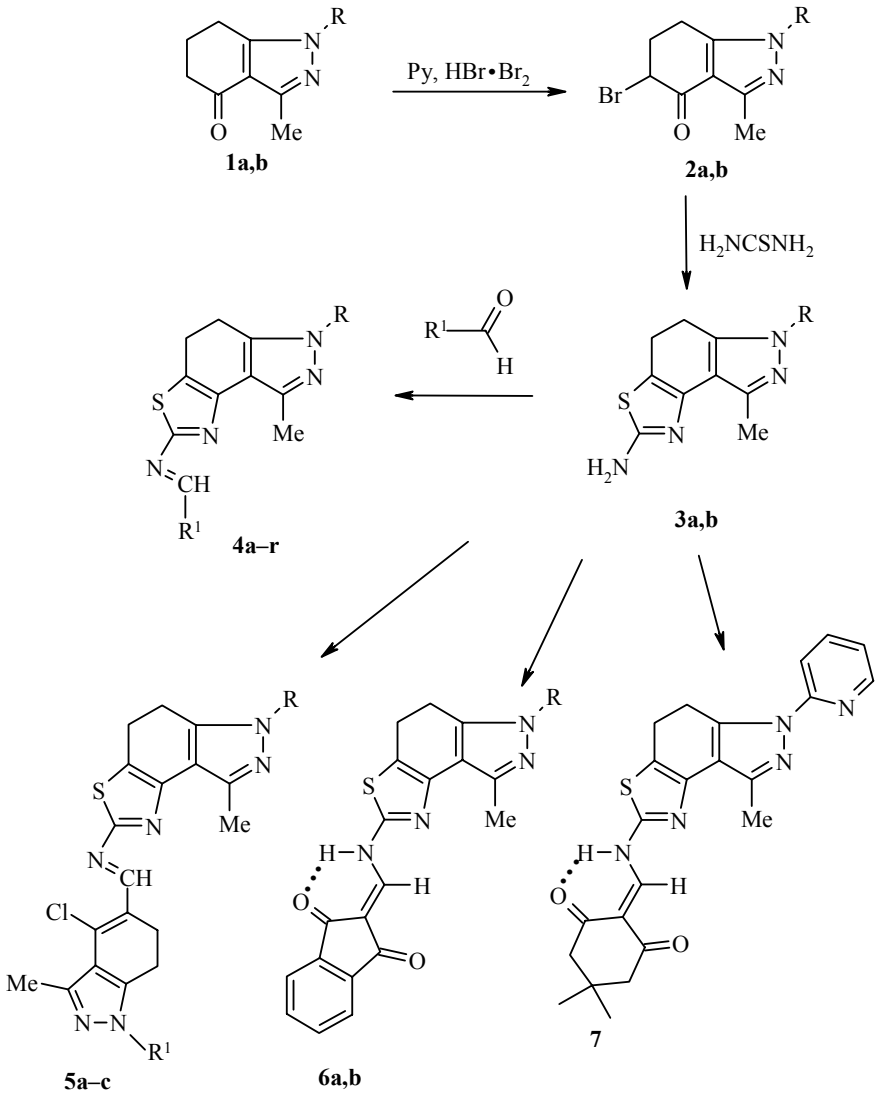

1-3, **6 a** R = 2-Py; **b** R = Ph; **4 a-g** R = 2-Py, **h-r** R = Ph; **a** R^1 = Ph; **b** R^1 = *p*-BrC_6H_4; **c** R^1 = *p*-FC_6H_4; **d** R^1 = 3-Py; **e** R^1 = 2-furyl; **f** R^1 = 2-thienyl; **g** R^1 = Ph–CH=CH–; **h** R^1 = *p*-BrC_6H_4; **i** R^1 = *p*-FC_6H_4; **j** R^1 = *p*-$Me_2NC_6H_4$; **k** R^1 = *p*-$MeOC_6H_4$; **l** R^1 = 3,4-$(MeO)_2C_6H_4$; **m** R^1 = 3,4-$O(CH_2)C_6H_3$; **n** R^1 = 3-Py; **o** R^1 = 4-Py; **p** R^1 = 2-furyl; **q** R^1 = 2-thienyl; **r** R^1 = Ph–CH=CH–; **5 a, b** R = Ph, **c** R = 2-Py, **a** R^1 = 2,4-$F_2C_6H_3$; **b**, **c** R^1 = 2-Py

TABLE 1. Characteristics of Compounds **4-7**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
1	2	3	4	5	6	7	8
4a	$C_{21}H_{17}N_5S$	67.77 / 67.90	4.60 / 4.61	18.92 / 18.86	8.40 / 8.63	177-179	81
4b	$C_{21}H_{16}BrN_5S$	55.81 / 56.00	3.52 / 3.58	17.61 / 17.74		250-251	66
4c	$C_{21}H_{16}FN_5S$	64.59 / 64.76	4.20 / 4.14	17.83 / 17.98		239-240	77
4d	$C_{20}H_{16}N_6S$	64.61 / 64.50	4.30 / 4.33	22.44 / 22.57	8.80 / 8.61	185-186	27

TABLE 1 (continued)

1	2	3	4	5	6	7	8
4e	$C_{19}H_{15}N_5OS$	63.01 63.14	4.14 4.18	19.30 19.38	8.90 8.87	184-185	94
4f	$C_{19}H_{15}N_5S_2$	60.33 60.45	3.95 4.01	18.50 18.56	17.20 16.99	211-212	56
4g	$C_{23}H_{19}N_5S$	69.40 69.50	4.77 4.82	17.75 17.62	8.20 8.07	187-188	75
4h	$C_{22}H_{17}BrN_4S$	58.61 58.80	3.76 3.81	12.32 12.47		192-193	44
4i	$C_{22}H_{17}FN_4S_2$	67.90 68.02	4.38 4.41	14.31 14.42		198-200	51
4j	$C_{24}H_{23}N_5S$	69.61 69.70	5.64 5.61	16.80 16.94	7.60 7.75	216-217	29
4k	$C_{23}H_{20}N_4OS$	68.84 68.97	4.89 5.03	14.06 13.99	8.10 8.01	174-175	25
4l	$C_{24}H_{22}N_4O_2S$	66.80 66.95	5.08 5.15	13.03 13.01	7.50 7.45	163-164	47
4m	$C_{23}H_{18}N_4O_2S$	66.52 66.65	4.30 4.38	13.40 13.52	7.60 7.74	183-185	24
4n	$C_{21}H_{17}N_5S$	67.71 67.90	4.48 4.61	18.66 18.86	8.50 8.63	176-177	41
4o	$C_{21}H_{17}N_5S$	67.77 67.90	4.55 4.61	18.69 18.86	8.70 8.63	202-205	27
4p	$C_{20}H_{16}N_4OS$	66.73 66.64	4.42 4.48	15.65 15.55	8.80 8.90	164-165	84
4q	$C_{20}H_{16}N_4S_2$	63.70 63.80	4.35 4.28	14.80 14.88	16.80 17.03	168-169	66
4r	$C_{24}H_{20}N_4S$	72.77 72.70	4.95 5.08	14.02 14.13	7.90 8.09	176-178	50
5a	$C_{30}H_{23}ClF_2N_6S$	62.68 62.88	4.00 4.03	14.55 14.67		213-215	53
5b	$C_{29}H_{24}ClN_7S$	64.80 64.73	4.45 4.50	18.10 18.22		173-176	74
5c	$C_{28}H_{23}ClN_8S$	62.31 62.39	4.34 4.30	20.71 20.79		261-263	83
6a	$C_{24}H_{17}N_5O_2S$	65.42 65.59	3.79 3.90	15.82 15.94	7.20 7.29	300-305	74
6b	$C_{25}H_{18}N_4O_2S$	68.36 68.48	4.09 3.14	12.62 12.78	7.20 7.31	272-273	81
7	$C_{23}H_{23}N_5O_2S$	63.60 63.72	5.30 5.35	16.11 16.16	7.50 7.40	224-225	93

TABLE 2. ^{1}H NMR Spectra of Products

Com-pound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)*
1	2
2a	2.47 (2H, m, CH_2); 2.53 (2H, s, CH_3); 3.53 (2H, m, CH_2); 4.46 (1H, t, ^3J = 3, CH); 7.21 (1H, m, Ar); 7.78-7.89 (2H, m, Ar); 7.91 (1H, dd, ^3J = 5, ^4J = 1.5, Ar)
3a	2.51 (3H, m, CH_3); 2.91 (2H, t, ^3J = 7, CH_2); 3.58 (2H, t, ^3J = 7, CH_2); 4.98 (2H, br. s, NH_2); 7.02 (1H, m, Ar); 7.71-7.91 (2H, m, Ar); 8.33 (1H, dd, ^3J = 5, ^4J = 1, Ar)
4a	2.62 (3H, s, CH_3); 3.09 (2H, t, ^3J = 7, CH_2); 3.64 (2H, t, ^3J = 7, CH_2); 7.07 (1H, dd. d, ^3J = 5, ^3J = 6, ^4J = 1, Ar); 7.02 (1H, m, Ar); 7.38-7.91 (7H, m, Ar); 8.31 (1H, dd, ^3J = 5, ^4J = 1, Ar); 8.91 (1H, s, =CH–)
4b	2.62 (3H, s, CH_3); 3.13 (2H, t, ^3J = 7, CH_2); 3.64 (2H, t, ^3J = 7, CH_2); 7.13 (1H, m, Ar); 7.49-7.96 (6H, m, Ar); 8.36 (1H, dd, ^3J = 5, ^4J = 1.5, Ar); 8.93 (1H, s, =CH–)
4c	2.62 (3H, s, CH_3); 3.09 (2H, t, ^3J = 7, CH_2); 3.64 (2H, t, ^3J = 7, CH_2); 7.09-7.85 (7H, m, Ar); 8.33 (1H, dd, ^3J = 5, ^4J = 1, Ar); 8.96 (1H, s, =CH–)
4d	2.58 (3H, s, CH_3); 3.13 (2H, t, ^3J = 7, CH_2); 3.58 (2H, t, ^3J = 7, CH_2); 7.07-8.31 (7H, m, Ar); 8.64 (1H, d, ^3J = 5, Ar); 9.02 (2H, s, =CH–)

TABLE 2 (continued)

1	2
4e	2.61 (3H, s, CH_3); 3.09 (2H, m, ^3J = 7, CH_2); 3.64 (2H, m, ^3J = 7, CH_2); 6.53 (1H, dd, ^3J = 5, ^4J = 1.5, Ar); 7.07 (2H, m, Ar); 7.60 (1H, d, ^4J = 1.5, Ar); 7.71 (1H, dd, ^3J = 7, ^4J = 1.5, Ar); 7.89 (1H, d, ^3J = 8, Ar); 8.33 (1H, dd, ^3J = 5, ^4J = 1.5, Ar); 8.87 (1H, s, =CH)
4f	2.61 (3H, s, CH_3); 3.07 (2H, t, ^3J = 7, CH_2); 3.58 (2H, t, ^3J = 7, CH_2); 7.11-7.93 (6H, m, Ar); 8.33 (1H, dd, ^3J = 5, ^4J = 1.5, Ar); 9.08 (1H, s, =CH–)
4g	2.65 (3H, s, CH_3); 3.09 (2H, t, ^3J = 7, CH_2); 3.64 (2H, t, ^3J = 7, CH_2); 7.13-7.86 (10H, m, Ar); 8.38 (1H, dd, ^3J = 5, ^4J = 1, Ar); 8.71 (1H, d, ^3J = 8, =CH–)
4h	2.61 (3H, s, CH_3); 3.02 (4H, s, $2CH_2$); 7.36 (5H, m, Ar); 7.51 (2H, m, ^3J = 8, Ar); 7.82 (2H, m, ^3J = 8, Ar); 8.89 (1H, s, =CH–)
4i	2.64 (3H, s, CH_3); 3.09 (4H, s, $2CH_2$); 7.11-7.47 (7H, m, Ar); 7.91 (2H, m, Ar); 8.93 (1H, s, =CH–)
4j	2.62 (3H, s, CH_3); 3.02 (4H, s, $2CH_2$); 3.06 (6H, s, $N(CH_3)_2$); 6.62 (2H, m, ^3J = 8, Ar); 7.38 (5H, m, Ar); 7.78 (2H, m, ^3J = 8, Ar); 8.71 (1H, s, =CH–)
4k	2.62 (3H, s, CH_3); 3.02 (4H, s, $2CH_2$); 3.82 (3H, s, CH_3); 6.89 (2H, m, ^3J = 8, Ar); 7.38 (5H, m, Ar); 7.89 (2H, m, ^3J = 8, Ar); 8.78 (1H, s, =CH–)
4l	2.62 (3H, s, CH_3); 3.04 (4H, s, $2CH_2$); 3.89 (3H, s, OCH_3); 3.94 (3H, s, OCH_3); 6.86 (1H, d, ^3J = 8, Ar); 7.41 (6H, m, Ar); 7.62 (1H, d, ^4J = 2, Ar); 8.81 (1H, s, =CH–)
4m	2.58 (3H, s, CH_3); 3.01 (4H, s, $2CH_2$); 5.96 (2H, s, CH_2); 6.82 (2H, m, ^3J = 8, Ar); 7.36-7.51 (6H, m, Ar); 8.78 (1H, s, =CH–)
4n	2.62 (3H, s, CH_3); 3.09 (4H, s, $2CH_2$); 7.38 (6H, m, Ar); 8.29 (1H, d. t, ^3J = 8, ^4J = 1.5, Ar); 8.69 (1H, dd, ^3J = 5, ^4J = 1.5, Ar); 9.01 (1H, d, ^4J = 1.5, Ar); 9.04 (1H, s, =CH–)
4o	2.62 (3H, s, CH_3); 3.13 (4H, s, $2CH_2$); 7.42 (5H, m, Ar); 7.81 (2H, m, ^3J = 5, Ar); 8.69 (2H, m, ^3J = 5, Ar); 9.06 (1H, s, =CH–)
4p	2.58 (3H, s, CH_3); 3.04 (4H, s, $2CH_2$); 6.56 (1H, dd, ^3J = 4, ^4J = 2, Ar); 7.07 (1H, d, ^3J = 4, Ar); 7.12-7.47 (5H, m, Ar); 7.61 (1H, d, ^4J = 2, Ar); 8.91 (1H, s, =CH–)
4q	2.58 (3H, s, CH_3); 3.02 (4H, s, $2CH_2$); 7.07-7.58 (8H, m, Ar); 9.07 (1H, s, =CH–)
4r	2.42 (3H, s, CH_3); 3.04 (4H, s, $2CH_2$); 7.16-7.53 (12H, m, Ar, 2=CH–); 8.71 (1H, d, ^3J = 9, =CH–)
5a	2.51 (3H, s, CH_3); 2.62 (4H, s, $2CH_2$); 2.63-3.02 (4H, m, $2CH_2$); 3.04 (3H, s, CH_3); 6.91-7.49 (8H, m, Ar); 9.16 (1H, s, =CH–)
5b	2.49 (3H, s, CH_3); 2.58 (3H, s, CH_3); 2.96 (4H, s, $2CH_2$); 2.98-3.38 (4H, m, $2CH_2$); 7.13-7.91 (8H, m, Ar); 8.36 (1H, dd, ^3J = 5, ^4J = 1.5, Ar); 9.16 (1H, s,=CH–)
5c	2.53 (3H, s, CH_3); 2.62 (3H, s, CH_3); 3.01-3.71 (8H, m, $4CH_2$); 7.13 (3H, m, Ar); 7.82 (4H, m, Ar); 8.36 (2H, m, Ar); 9.16 (1H, s, =CH–)
6a	2.61 (3H, s, CH_3); 3.04 (2H, t, ^3J = 7, CH_2); 3.64 (2H, t, ^3J = 7, CH_2); 7.11 (1H, m, Ar); 7.82 (6H, m, Ar); 8.35 (1H, m, Ar); 8.42 (1H, d, ^3J = 12, =CH–); 11.36 (1H, d, ^3J = 12, NH)
6b	2.63 (3H, s, CH_3); 3.08 (4H, s, $2CH_2$); 7.43-7.78 (9H, m, Ar); 8.52 (1H, d, ^3J = 12, =CH–); 11.39 (1H, d, ^3J = 12, NH)
7	1.02 (6H, s, $2CH_3$); 2.36 (2H, s, CH_2); 2.38 (2H, s, CH_2); 2.51 (3H, s, CH_3); 3.04 (2H, t, ^3J = 7, CH_2); 3.62 (2H, t, ^3J = 7, CH_2); 7.04 (1H, dd. d, ^2J = 5, ^3J = 7, ^4J = 1.5, Ar); 7.69 (1H, d. t, ^3J = 7, ^4J = 1.5, Ar); 7.89 (1H, dd, ^3J = 7, ^4J = 1.5, Ar); 8.31 (1H, dd, ^3J = 5, ^4J = 1.5, Ar); 8.67 (1H, d, ^3J = 13, =CH–); 12.16 (1H, d, ^3J = 13, NH)

* The ^{1}H NMR spectra of **4e, 4i, 4l, 4p,** and **4q** were taken in DMSO-d_6, the spectra of the other compounds were taken in $CDCl_3$.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WH-90/DS at 90 MHz using TMS as the internal standard. The IR spectra were taken on a Specord IR-75 spectrometer for suspensions in vaseline oil at 1800-1500 cm^{-1} and in hexachlorobutadiene at 3600-2000 cm^{-1}.

The aldehyde samples used were supplied by Acros. The characteristics of **4-7** are given in Tables 1 and 2.

Our previous procedure [2] was used to prepare **1a**, while 2-amino-6-phenyl-7,8-dihydroindazolo-[4,5-*d*]thiazole was prepared by a procedure described in our earlier work [1].

5-Bromo-3-methyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole (2a). A solution of pyridinium bromide perbromide (3.20 g, 10 mmol) in acetic acid (50 ml) was added to a solution of indazole **1a** (2.27 g, 10 mmol) in acetic acid (30 ml) and heated at reflux for 20 min. Then, water (100 ml) was added to the hot reaction mixture. The tarry product, which rapidly solidifies, was filtered off and recrystallized from 2:1 ethanol–water to give 1.71 g (56%) of **2a**; mp 121-122°C. IR spectrum, ν, cm^{-1}: 1680 (C=O). Found, %: C 51.11; H 4.02; Br 25.90; N 13.55. $C_{13}H_{12}BrN_3O$. Calculated, %: C 51.00; H 3.95; Br 26.10; N 13.73.

2-Amino-4-methyl-6-(2-pyridyl)-7,8-dihydroindazolo[4,5-*d*]thiazole (3a). A mixture of bromoketone **2a** (1.54 g, 5 mmol) and thiourea (0.38 g, 5 mmol) in ethanol (40 ml) was heated at reflux for 14 h and then cooled. Water (80 ml) and concentrated ammonium hydroxide (2 ml) was added. The precipitate formed was filtered off and recrystallized from 2:1 ethanol–water to give 1.02 g (72%) of **3a**; mp 106-108°C. IR spectrum, ν, cm^{-1}: 3320, 3410 (NH). Found, %: C 59.22; H 4.50; N 24.60; S 11.20. $C_{14}H_{13}N_5S$. Calculated, %: C 59.34; H 4.62; N 24.72; S 11.32.

2-Benzalamino- (4a), 2-(4-Bromobenzal)amino- (4b), 2-(4-Fluorobenzal)amino- (4c), 2-(3-Pyridylmethylene)amino- (4d), 2-(2-Furylmethylene)amino- (4e), 2-(2-Thienylmethylene)amino- (4f), 2-(3-Phenyl-2-propen-1-ylidene)amino- (4g) 4-methyl-6-(2-pyridyl)-7,8-dihydroindazolo[4,5-*d*]thiazoles, 2-(4-Bromobenzal)amino- (4h), 2-(4-Fluorobenzal)amino- (4i), 2-(4-Dimethylaminobenzal)amino- (4j), 2-(4-Methoxybenzal)amino- (4k), 2-(3,4-Dimethoxybenzal)amino- (4l), 2-(3,4-Methylenedioxybenzal)-amino- (4m), 2-(3-Pyridylmethylene)amino- (4n), 2-(4-Pyridylmethylene)amino- (4o), 2-(2-Furyl-methylene)amino- (4p), 2-(2-Thienylmethylene)amino- (4q), and 2-(3-Phenyl-2-propen-1-ylidene)amino- (4r) 4-methyl-6-phenyl-7,8-dihydroindazolo[4,5-*d*]thiazoles. Hot solutions of the corresponding aminothiazole (**3a** or **3b**) (2 mmol) in ethanol (20 ml) and an equimolar amount of aldehyde in ethanol (10 ml) were combined and heated at reflux for 4 h. The reaction mixture was left for 24 h in a refrigerator. The precipitate of **4** was filtered off and recrystallized, **4a,d,k-r** from ethanol, **4b,c,h-j** from DMF,and **4e-g** from ethanol–DMF.

2-[4-Chloro-1-(2,4-difluorophenyl)-3-methyl-6,7-dihydroindazol-5-yl]methyleneamino-4-methyl-6-phenyl- (5a), 2-[4-Chloro-3-methyl-1-(2-pyridyl)-6,7-dihydroindazol-5-yl]methyleneamino-4-methyl-6-phenyl- (5b), and 2-[4-Chloro-3-methyl-1-(2-pyridyl)-6,7-dihydroindazol-5-yl]methylenamino-4-methyl-6-(2-pyridyl)- (5c) 7,8-dihydroindazolo[4,5-*d*]thiazoles. Hot solutions of the corresponding amine **3** and 1-substituted 4-chloro-5-formyl-3-methyl-6,7-dihydroindazole [7] were combined and heated at reflux for 1 h. The reaction mixtures were left stand in a refrigerator for 24 h, filtered off and recrystallized, **5b**,**c** from DMF and **5a** from ethanol–DMF.

2-[4-Methyl-6-(2-pyridyl)- (6a) and 2-[4-Methyl-6-phenyl- (6b) indazolo[4,5-*d*]thiazol-2-yl]amino-methylene-1,3-indanediones, 2-[4-Methyl-6-(2-pyridyl)indazolo[4,5-*d*]thiazol-2-yl]aminomethylene-5,5-dimethyl-1,3-cyclohexanedione (7). Hot solutions of corresponding amine **3** and 2-formyl-1,3-cyclohexanedione were combined and heated at reflux for 10-15 min. The reaction mixtures were cooled and filtered. Diones **6a**,**b** were obtained by recrystallization from DMF, while dione **7** was obtained by recrystallization from ethanol–DMF.

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