A Convenient Synthesis of Functionalized Indenopyrazolones from Indan-1,2,3-trione, Benzaldehydes, and Phenylhydrazine

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A synthesis of *cis*-3-aryl-3a,8b-dihydro-3a,8b-dihydroxy-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-ones in good yields from the sequential reaction between benzaldehydes, phenylhydrazine, and indan-1,2,3-trione in MeCN is described (*Scheme 1*).

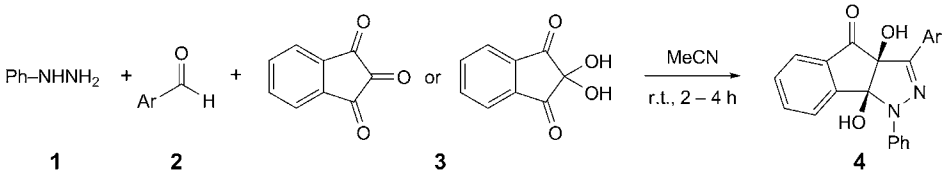
Introduction. – The pyrazole ring is an important structural motif found in several pharmaceutically active compounds [1][2]. Pyrazole derivatives exhibit diverse bioactivities such as anti-anxiety [3], anti-inflammatory [4], and antitumor activity [5]. Thus, the synthesis of pyrazole and its fused derivatives is of interest. The common methods for the preparation of pyrazoles are the condensation reaction of *N*-arylhydrazines with a variety of 1,3-dicarbonyl compounds [6], and the 1,3-dipolar cycloadditions of diazo compounds [7] or nitrile imines [8–10] onto triple bonds.

Results and Discussion. – As part of our current studies on the development of new routes in heterocyclic synthesis [9–11], we report the results of our studies involving the reaction of phenylhydrazones, derived from phenylhydrazine (**1**) and bezaldehydes **2**, with indan-1,2,3-trione (=1*H*-indene-1,2-3-trione; **3**) in MeCN, which constitutes a synthesis of *cis*-3-aryl-3a,8b-dihydro-3a,8b-dihydroxy-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-ones **4** in good yields (*Scheme 1*).

The ^{1}H- and ^{13}C-NMR spectra of the crude products clearly indicated the formation of indenopyrazolones **4**. The mass spectra of these compounds displayed molecular-ion peaks at the appropriate *m*/*z* values (see *Exper. Part*). The structures of compounds **4a**–**4i** were deduced from their IR and ^{1}H- and ^{13}C-NMR spectra (*cf. Exper. Part*). For example, the ^{1}H-NMR spectrum of **4a** exhibited two single sharp lines readily recognized as arising from two OH groups (δ(H) 6.15 and 6.17), together with characteristic signals for the aromatic H-atoms. The ^{13}C-NMR spectrum of **4a** showed 18 distinct signals in agreement with the proposed structure. The ^{1}H- and ^{13}C-NMR spectra of **4b**–**4i** were similar to those of **4a**, except for the Ar groups, which exhibited characteristic signals with appropriate chemical shifts.

Unambiguous evidence for the structure and configuration of **4d** was obtained from a single-crystal X-ray analysis. An ORTEP [12] diagram of **4d** is shown in the *Figure*. The molecular structure is further stabilized by an intramolecular H-bond of the type

Scheme 1



	Ar	Product	Yield [%]
2a	Ph	**4a**	84
2b	4-MeO–C_6H_4	**4b**	80
2c	4-Me–C_6H_4	**4c**	74
2d	4-Cl–C_6H_4	**4d**	88
2e	4-Br–C_6H_4	**4e**	90
2f	4-NO_2–C_6H_4	**4f**	80
2g	3-NO_2–C_6H_4	**4g**	78
2h	2-OH–C_6H_4	**4h**	78
2i	2-OH,3-$NO_2C_6H_3$	**4i**	76

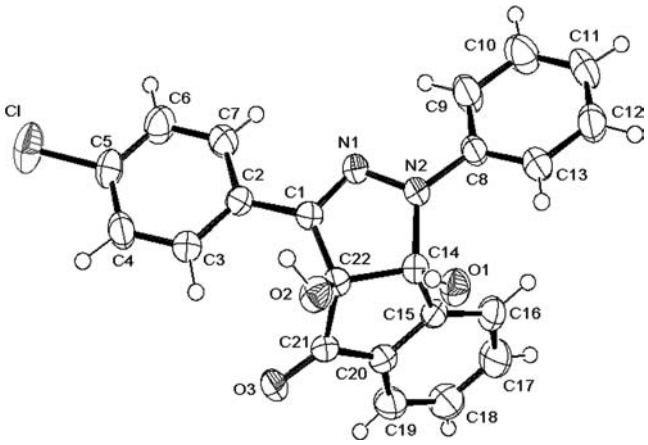


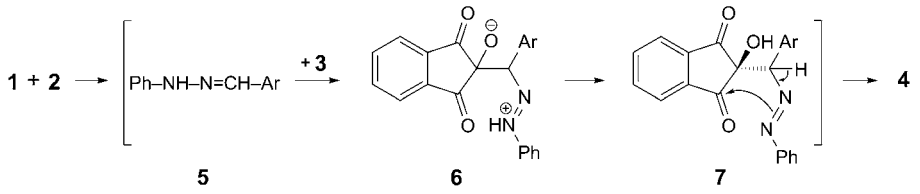
Fig. 1. *X-Ray crystal structure of* **4d**. ORTEP-III Plot [12]; arbitrary atom numbering.

O(1)–H(14) ··· O(2), with $d(O(1) \cdots O(2)) = 2.684(3)$ Å and $\varphi(O(1)\text{–}H(14) \cdots O(2)) = 115(2)^\circ$. Moreover, the molecules are arranged in helices along the 2_1 axes, *via* an intermolecular H-bond of the type O(2)–H(15) ··· O(3), with $d(O(2) \cdots O(3)) = 2.732(3)$ Å and $\varphi(O(2)\text{–}H(15) \cdots O(3)) = 170(2)^\circ$. The structure of **4d** deduced from the crystallographic experiment, can be applied by analogy, to the other products **4** on account of their NMR-spectroscopic similarities. For details of the structure determination and refinement, see *Exper. Part*.

A mechanistic rationalization for the reaction leading to **4** is given in *Scheme 2*. The initial event is the formation of phenylhydrazone **5**, which attacks indan-1,2,3-trione to afford the zwitterionic intermediate **6**. Its tautomer **7** undergoes an intramolecular nucleophilic addition reaction, which affords **4** by a H-atom-transfer reaction.

In summary, we reported a sequential transformation involving phenylhydrazine, benzaldehydes, and indan-1,2,3-trione, which afforded a new route to the synthesis of

Scheme 2



cis-3-aryl-3a,8b-dihydro-3a,8b-dihydroxy-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-ones. Due to the presence of transformable functionalities in these products, they are potentially valuable for further synthetic manipulations.

Experimental Part

General. Compounds **1**–**3** were obtained from *Merck* and used without further purification. All chemicals were used as received from the appropriate supplies. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-500 Avance* instrument; in $CDCl_3$ at 500.1 (^1H) and 125.7 MHz (^{13}C); δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS (70 eV): *Finnigan-MAT-8430* mass spectrometer; in *m*/*z*. Elemental analyses (C, H, N): *Heraeus-CHN-O-Rapid* analyzer.

Compounds **4**: *General Procedure.* A mixture of **1** (0.214 g, 2 mmol) and aldehyde **2** (2 mmol) was stirred at r.t. in anh. MeCN (10 ml). After 30 min, indan-1,2,3-trione (**3**; 0.320 g, 2 mmol) was added, and the mixture was stirred for 2–4 h. After completion of the reaction (TLC (AcOEt/hexane 2:1) monitoring), the precipitate was collected by filtration and washed with cold Et_2O.

cis-*3a,8b-Dihydro-3a,8b-dihydroxy-1,3-diphenylindeno[1,2-*c*]pyrazol-4(1*H*)-one* (**4a**): Yield 0.60 g (84%). Yellow powder. M.p. 220–223°. IR (KBr): 3428, 3055, 1727, 1466. ^1H-NMR: 6.15 (*s*, OH); 6.17 (*s*, OH); 7.11 (*d*, $^3J = 7.9$, CH); 7.22 (*t*, $^3J = 7.6$, CH); 7.32 (*t*, $^3J = 7.6$, 2 CH); 7.41 (*t*, $^3J = 7.6$, CH); 7.50 (*t*, $^3J = 7.6$, CH); 7.51–7.64 (*m*, 5 CH); 8.19 (*d*, $^3J = 7.9$, 2 CH); 8.46 (*d*, $^3J = 7.9$, CH). ^{13}C-NMR: 89.4 (C); 96.9 (C); 118.4 (2 CH); 121.6 (CH); 122.8 (CH); 123.3 (CH); 124.2 (CH); 126.0 (2 CH); 129.4 (2 CH); 130.8 (CH); 130.9 (C); 132.9 (2 CH); 133.4 (CH); 137.0 (C); 139.7 (C); 142.2 (C); 147.7 (C); 196.8 (C=O). EI-MS: 356 (3, M^+), 339 (20), 279 (32), 185 (35), 168 (80), 77 (100), 27 (30). Anal. calc. for $C_{22}H_{16}N_2O_3$ (356.37): C 74.15, H 4.53, N 7.86; found: C 74.53, H 4.64, N 7.77.

cis-*3a,8b-Dihydro-3a,8b-dihydroxy-3-(4-methoxyphenyl)-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one* (**4b**): Yield 0.61 g (80%). Yellow powder. M.p. 211–214°. IR (KBr): 3424, 3280, 1706, 1594. ^1H-NMR: 3.68 (*s*, MeO); 6.13 (*s*, OH); 6.21 (*s*, OH); 6.75 (*d*, $^3J = 8.4$, 2 CH); 6.87 (*t*, $^3J = 7.1$, CH); 7.19 (*t*, $^3J = 7.5$, 2 CH); 7.28 (*t*, $^3J = 7.1$, CH); 7.39 (*t*, $^3J = 7.3$, CH); 7.52 (*d*, $^3J = 7.8$, CH); 7.57 (*d*, $^3J = 7.5$, CH); 7.64 (*d*, $^3J = 7.9$, 2 CH); 8.00 (*d*, $^3J = 8.4$, 2 CH). ^{13}C-NMR: 55.5 (MeO); 90.0 (C); 96.4 (C); 113.9 (2 CH); 117.9 (2 CH); 122.2 (CH); 123.8 (CH); 124.2 (C); 125.9 (CH); 128.7 (2 CH); 129.2 (2 CH); 130.5 (CH); 135.2 (C); 136.6 (CH); 142.9 (C); 143.2 (C); 147.9 (C); 160.2 (C); 197.4 (C=O). EI-MS: 386 (70, M^+), 355 (20), 279 (30), 202 (35), 107 (15), 77 (100), 40 (32). Anal. calc. for $C_{23}H_{18}N_2O_4$ (386.40): C 71.49, H 4.70, N 7.25; found: C 71.83, H 4.75, N 7.34.

cis-*3a,8b-Dihydro-3a,8b-dihydroxy-3-(4-methylphenyl)-1-phenyl-indeno[1,2-*c*]pyrazol-4(3a*H*)-one* (**4c**): Yield 0.54 g (74%). Yellow powder. M.p. 248–250°. IR (KBr): 3435, 3267, 1716, 1596. ^1H-NMR: 2.37 (*s*, Me); 6.14 (*s*, OH); 6.17 (*s*, OH); 7.09 (*t*, $^3J = 7.8$, CH); 7.28 (*d*, $^3J = 7.9$, 2 CH); 7.38 (*t*, $^3J = 7.8$, 2 CH); 7.51 (*t*, $^3J = 7.9$, CH); 7.57 (*t*, $^3J = 8.0$, CH); 7.75 (*d*, $^3J = 7.9$, CH); 7.91 (*d*, $^3J = 7.9$, 2 CH); 8.07 (*d*, $^3J = 7.7$, 2 CH); 8.44 (*d*, $^3J = 7.9$, CH). ^{13}C-NMR: 21.4 (Me); 89.3 (C); 95.4 (C); 126.1 (CH); 126.3 (2 CH); 124.4 (2 CH); 129.0 (CH); 129.2 (CH); 129.4 (2 CH); 129.6 (CH); 129.7 (2 CH); 130.7 (C); 134.6 (CH); 136.8 (C); 138.4 (C); 140.4 (C); 142.2 (C); 146.7 (C); 197.4 (C=O). EI-MS: 370 (3, M^+), 355 (20), 293 (76), 279 (35), 202 (15), 91 (100), 77 (30). Anal. calc. for $C_{23}H_{18}N_2O_3$ (370.40): C 74.58, H 4.90, N 7.56; found: C 74.22, H 5.01, N 7.50.

cis-*3-(4-Chlorophenyl)-3a,8b-dihydro-3a,8b-dihydroxy-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one* (**4d**): Yield 0.68 g (88%). Yellow crystals. M.p. 233–236°. IR (KBr): 3453, 3262, 1697, 1591. ^{1}H-NMR: 6.09 (*s*, OH); 6.12 (*s*, OH); 7.03 (*t*, ^3J = 7.8, CH); 7.31 (*t*, ^3J = 7.8, 2 CH); 7.31 (*d*, ^3J = 7.8, 2 CH); 7.41 (*t*, ^3J = 7.8, CH); 7.52 (*t*, ^3J = 7.8, CH); 7.63 (*d*, ^3J = 7.3, CH); 7.71 (*d*, ^3J = 7.0, CH); 7.76 (*d*, ^3J = 7.1, 2 CH); 8.11 (*d*, ^3J = 7.7, 2 CH). ^{13}C-NMR: 89.8 (C); 96.6 (C); 118.2 (2 CH); 122.8 (CH); 124.2 (CH); 126.0 (CH); 128.4 (2 CH); 128.7 (2 CH); 129.4 (2 CH); 130.1 (C); 130.7 (CH); 134.5 (C); 135.3 (C); 136.9 (CH); 142.5 (C); 142.6 (C); 147.7 (C); 197.0 (C=O). EI-MS: 390 (60, M^+), 355 (20), 313 (28), 245 (32), 202 (15), 111 (100), 77 (30). Anal. calc. for $C_{22}H_{15}ClN_2O_3$ (390.81): C 67.61, H 3.87, N 7.17; found: C 67.89, H 3.94, N 7.24.

X-Ray Crystal-Structure Determination of **4d**. $C_{22}H_{15}ClN_2O_3$, M_r 390.81, crystal size 0.14 × 0.11 × 0.08 mm; crystal system: monoclinic, a = 8.9510(10), b = 9.1550(10), c = 22.136(2) Å, β = 94.680(10)°; space group $P2_1/c$; Z = 4, V = 1807.9(3) Å^3, $D_{calc.}$ = 1.436 Mg/m^3; 3855 reflections collected with a *Bruker-P4* diffractometer (R_{int} = 0.0336), MoK_α radiation (λ 0.71073 Å), T 293(2) K. The structure was solved by direct methods and refined on F^2 with the SHELX97 package. All atoms were located by difference *Fourier* maps. The non-H-atoms were refined anisotropically and the H-atoms isotropically. Final indices ($I > 2\sigma$ (I)): R_1 = 0.0517, wR_2 = 0.1056, g.o.f. = 0.991. CCDC-864848 contains the supplementary crystallographic data for **4d**. These data can be obtained, free of charge, *via* http://www.ccdc.cam.ac.uk/data_request/cif.

cis-*3-(4-Bromophenyl)-3a,8b-dihydro-3a,8b-dihydroxy-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one* (**4e**): Yield 0.78 g (90%). Yellow powder. M.p. 221–225°. IR (KBr): 3442, 3256, 1695, 1587. ^{1}H-NMR: 6.04 (*s*, OH); 6.06 (*s*, OH); 7.05 (*t*, ^3J = 7.8, CH); 7.35 (*t*, ^3J = 7.3, 2 CH); 7.45 (*t*, ^3J = 7.9, CH); 7.47 (*d*, ^3J = 7.9, 2 CH); 7.54 (*t*, ^3J = 7.1, CH); 7.65 (*d*, ^3J = 7.6, CH); 7.73 (*d*, ^3J = 7.5, CH); 7.75 (*d*, ^3J = 7.7, 2 CH); 8.06 (*d*, ^3J = 7.9, 2 CH). ^{13}C-NMR: 89.7 (C); 96.6 (C); 118.2 (2 CH); 122.9 (CH); 124.2 (CH); 126.0 (CH); 128.7 (2 CH); 129.4 (2 CH); 130.5 (C); 130.7 (CH); 131.7 (2 CH); 135.3 (C); 136.8 (CH); 136.9 (C); 142.1 (C);142.5 (C); 147.6 (C); 196.9 (C=O). EI-MS: 435 (4, M^+), 355 (22), 417 (32), 279 (34), 154 (75), 104 (30), 78 (100). Anal. calc. for $C_{22}H_{15}BrN_2O_3$ (435.27): C 60.71, H 3.47, N 6.44; found: C 60.44, H 3.53, N 6.51.

cis-*3a,8b-Dihydro-3a,8b-dihydroxy-3-(4-nitrophenyl)-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one* (**4f**): Yield 0.64 g (80%). Orange powder. M.p. 241–244°. IR (KBr): 3401, 3042, 1719, 1590. ^{1}H-NMR: 6.18 (*s*, OH); 6.20 (*s*, OH); 7.12 (*t*, ^3J = 7.4, CH); 7.39 (*t*, ^3J = 8.4, 2 CH); 7.54 (*t*, ^3J = 7.6, CH); 7.62 (*d*, ^3J = 6.3, CH); 7.63 (*t*, ^3J = 6.3, CH); 7.77 (*d*, ^3J = 7.6, CH); 7.81 (*d*, ^3J = 7.7, 2 CH); 8.23 (*d*, ^3J = 7.1, 2 CH); 8.37 (*d*, ^3J = 7.2, 2 CH). ^{13}C-NMR: 89.7 (C); 97.6 (C); 118.4 (2 CH); 122.8 (2 CH); 123.0 (CH); 123.1 (CH); 125.3 (CH); 126.8 (2 CH); 128.6 (2 CH); 130.3 (CH); 134.7 (C); 136.3 (CH); 137.9 (C); 140.4 (C); 142.0 (C); 146.9 (C); 147.5 (C); 197.5 (C=O). EI-MS: 401 (4, M^+), 383 (10), 223 (20), 179 (80), 104 (70), 76 (100), 50 (40). Anal. calc. for $C_{22}H_{15}N_3O_5$ (401.37): C 65.83, H 3.78, N 10.49; found: C 66.31, H 3.71, N 10.58.

cis-*3a,8b-Dihydro-3a,8b-dihydroxy-3-(3-nitrophenyl)-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one* (**4g**): Yield 0.62 g (78%). Orange powder. M.p. 242–244°. IR (KBr): 3460, 1720, 1593, 1503. ^{1}H-NMR: 6.24 (*s*, OH); 6.34 (*s*, OH); 7.06 (*t*, ^3J = 7.4, CH); 7.35 (*t*, ^3J = 7.5, 2 CH); 7.45 (*t*, ^3J = 7.4, CH); 7.50 (*t*, ^3J = 8.0, CH); 7.55 (*t*, ^3J = 6.3, CH); 7.65 (*d*, ^3J = 7.9, CH); 7.73 (*d*, ^3J = 7.6, CH); 7.79 (*d*, ^3J = 7.9, 2 CH); 8.06 (*d*, ^3J = 8.1, CH); 8.51 (*d*, ^3J = 7.8, CH); 8.97 (*s*, CH). ^{13}C-NMR: 89.4 (C); 96.9 (C); 118.4 (2 CH); 121.6 (CH); 122.8 (CH); 123.3 (CH); 124.2 (CH); 126.0 (CH); 129.4 (2 CH); 129.5 (CH); 130.8 (CH); 132.9 (CH); 133.4 (C); 135.0 (C); 137.0 (CH); 140.7 (C); 142.2 (C); 147.5 (C); 147.7 (C); 196.8 (C=O). EI-MS: 401 (3, M^+), 383 (10), 223 (20), 179 (80), 104 (70), 76 (100), 50 (40). Anal. calc. for $C_{22}H_{15}N_3O_5$ (401.37): C 65.83, H 3.78, N 10.49; found: C 66.28, H 3.84, N 10.58.

cis-*3a,8b-Dihydro-3a,8b-dihydroxy-3-(2-hydroxyphenyl)-1-phenylindeno[1,2-*c*]pyrazol-4(1*H*)-one* (**4h**): Yield 0.58 g (78%). Orange powder. M.p. 190–193°. IR (KBr): 3424, 1756, 1536, 1459. ^{1}H-NMR: 4.50 (*s*, OH); 6.15 (*s*, OH); 6.18 (*s*, OH); 6.96 (*t*, ^3J = 7.4, 2 CH); 7.19 (*t*, ^3J = 7.3, CH); 7.24 (*t*, ^3J = 7.7, CH); 7.35–7.41 (*m*, 3 CH); 7.50 (*t*, ^3J = 7.4, CH); 7.55 (*d*, ^3J = 7.6, CH); 7.59 (*d*, ^3J = 8, 2 CH), 7.78 (*d*, ^3J = 7.1, CH), 8.05 (*d*, ^3J = 7.8, CH). ^{13}C-NMR: 89.5 (C); 94.1 (C); 116.6 (CH); 118.5 (2 CH); 119.0 (CH); 123.9 (CH); 124.3 (CH); 125.6 (CH); 127.8 (CH); 129.3 (2 CH); 130.5 (CH); 130.9 (CH); 134.6 (C); 134.8 (C); 137.1 (CH); 141.2 (C); 144.7 (C); 146.1 (C); 157.3 (C); 197.0 (C=O). MS: 372 (30, M^+), 306 (70), 224 (25), 105 (30), 91 (60), 69 (90), 57 (100). Anal. calc. for $C_{22}H_{16}N_2O_4$ (372.37): C 70.96, H 4.33, N 7.52; found: C 71.43, H 4.40, N 7.58.

cis-*3a,8b-Dihydro-3a,8b-dihydroxy-3-(2-hydroxy-3-nitrophenyl)-1-phenylindeno[1,2-c]pyrazol-4(1H)-one* (**4i**): Yield 0.63 g (76%). Orange powder. M.p. 195–200°. IR (KBr): 3324, 1726, 1596, 1489. ^{1}H-NMR: 4.50 (*s*, OH); 6.18 (*s*, OH); 6.20 (*s*, OH); 6.96–6.99 (*m*, 3 CH); 7.18 (*t*, ^3J = 6.3, CH); 7.31 (*t*, ^3J = 6.3, 2 CH); 7.37–7.40 (*m*, 2 CH); 7.54 (*d*, ^3J = 7.1, CH); 7.55 (*d*, ^3J = 7.1, CH); 7.82 (*t*, ^3J = 7.2, CH), 7.90 (*d*, ^3J = 7.2, CH). ^{13}C-NMR: 89.0 (C); 94.2 (C); 117.2 (CH); 118.9 (2 CH); 121.6 (CH); 124.5 (CH); 124.7 (CH); 124.9 (CH); 125.6 (CH); 128.6 (2 CH); 131.6 (CH); 132.6 (C); 134.4 (C); 137.5 (CH); 140.6 (C); 142.6 (C); 142.8 (C); 146.3 (C); 162.4 (C); 196.2 (C=O). MS: 417 (4, M^+), 400 (32), 371 (20), 279 (100), 168 (40), 77 (35), 45 (35). Anal. calc. for $C_{22}H_{15}N_3O_6$ (417.37): C 63.31, H 3.62, N 10.07; found: C 62.91, H 3.74, N 10.15.

REFERENCES

[1] L. F. Tietze, A. Steinmetz, F. Balkenhohl, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1303.
[2] P. Brooking, A. Doran, P. Grimsey, N. W. Hird, W. S. MacLachlan, M. Vimil, *Tetrahedron Lett.* **1999**, *40*, 1405.
[3] D. J. Wustrow, T. Capiris, R. Rubin, J. A. Knobelsdorf, H. Akunne, M. D. Davis, R. Mackenzic, T. A. Pugsley, K. T. Zoski, T. G. Heffiner, L. D. Wise, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2067.
[4] G. Menozzi, L. Mosti, P. Fossa, F. Mattioli, M. Ghia, *J. Heterocycl. Chem.* **1997**, *34*, 963.
[5] G. B. Onoa, V. Moreno, M. Font-Bardia, X. Solans, J. M. Pérez, C. Alonso, *J. Inorg. Biochem.* **1999**, *75*, 205.
[6] V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *J. Org. Chem.* **2003**, *68*, 5381.
[7] B. C. Bishop, K. M. J. Brands, A. D. Gibb, D. J. Kennedy, *Synthesis* **2004**, 43.
[8] J. C. Clovis, W. Fliege, R. Huisgen, *Chem. Ber.* **1983**, *116*, 3062.
[9] I. Yavari, G. Khalili, A. Mirzaei, *Helv. Chim. Acta* **2010**, *93*, 277.
[10] I. Yavari, G. Khalili, *Synlett* **2010**, 1862.
[11] I. Yavari, L. Moradi, *Helv. Chim. Acta* **2006**, 89, 1942.
[12] A. M. N. Burnett, C. K. Johnson, 'Oak Ridge National Laboratory Report ORNL-6895', 1996.

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