Monatshefte für Chemie 131, 475–486 (2000)

Monatshefte für Chemie
Chemical Monthly

Synthesis of Pyrazoles from 1-Acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofurans

Jacek G. Sośnicki

Technical University, Institute of Fundamental Chemistry, PL-71065 Szczecin, Poland

Summary. 1-Acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofurans were found to be useful precursors for pyrazole synthesis. In the reaction with hydrazine monohydrate they yielded 3-(2-(α-hydroxyisopropyl)-phenyl) substituted NH-pyrazoles, whereas using alkyl- or arylhydrazine gave access to 5-(2-(α-hydroxyisopropyl)-phenyl) substituted N*R*-pyrazoles with good regioselectivity. Treatment with orthophosphoric acid led to C,N-fused and C,C-fused pyrazoles, respectively.

Keywords. Heterocycles; Ring chain transformation reactions; Pyrazoles; Regioselectivity; Intramolecular alkylation of pyrazoles.

Introduction

Acylenol ethers as 1,3-dicarbonyl heteroanalogs are useful reagents for the synthesis of different types of heterocycles in the reaction with binucleophiles. If at least one electrophilic center of the 1,3-dielectrophilic acylenol ethers is a part of a ring system, *e.g.* like in 3-acyl-4,5-dihydrofurans or 5-acyl-3,4-dihydro-2*H*-pyran, the reaction with binucleophiles has been shown to give access to chain functionalized heterocycles [1–5]. The synthesis of side chain functionalized alkylheterocycles, matching to the general concept of the ring chain transformation reaction of 1,3-dicarbonyl heteroanalogs, has been reviewed recently [5]. One of the possible mechanisms consists of the condensation of the carbonyl moiety with one nucleophilic site, β-addition of the other nucleophilic position, and final opening of the spiro intermediate formed.

In this context, 1-acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofurans (**1a–c**) as bridged acylenol ethers were expected to be promising starting materials for the synthesis of heterocycles by treatment with binucleophiles. In the course of previous studies on reactions with hydroxylamine, the synthesis of spiroisoxazolines has been reported [6]. For further exploring the synthetic potential of 1-acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofurans (**1**) we now focused our interest on the synthesis of N,N-heterocycles achieved by reaction with hydrazine derivatives.

Result and Discussion

First investigations with hydrazine monohydrate revealed that, unlike to the formation of spiro products obtained with hydroxylamine, 1-formylmethylene-3,3-

dimethyl-1,3-dihydroisobenzofuran (**1a**) gave a ring chain transformation to the pyrazole **3h** with a 3-(2-(α-hydroxyisopropyl)-phenyl) substituent at the heterocyclic ring (Scheme 1). This result prompted us to extend our study to 1-acetylmethylene (**1b**) and 1-benzoylmethylene- (**1c**) derivatives of 3,3-dimethyl-1,3-dihydroisobenzofuran on the one hand and methyl and arylhydrazine derivatives on the other hand.

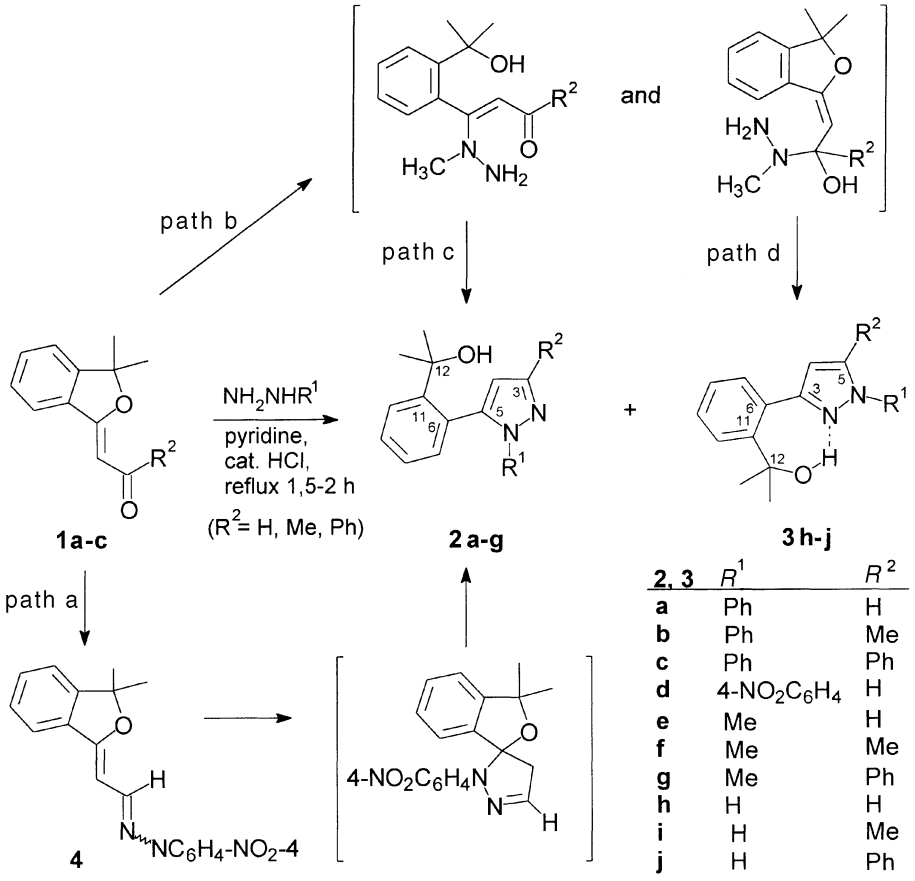
Since in the preparation of pyrazoles from masked 1,3-dicarbonyl compounds different electrophilicity at C-1 and C-3 of the carbonyl reagent and different nucleophilicity of the two nitrogen atoms of hydrazine determine the formation of different regioisomers [7], the regioselectivity of the investigated reaction had to be taken into consideration.

As far as regioselectivity is concerned, regioisomers **2** highly dominated when aryl hydrazines were used (Table 1). Under the same conditions, methylhydrazine

Table 1. Regioselectivities for compounds **2**, **3**

2,**3**	R^1	R^2	Ratio of regioisomers[a] **2** : **3**		Procedure Yield (%)[b] **2**	**3**
a	Ph	H	100	0	A 76(92)	–
b	Ph	Me	100	0	A 65(94)	–
c	Ph	Ph	87	13[c]	A(88) 65	14
d	4-$NO_2C_6H_4$	H	100	0	A 68(90)	–
e	Me	H	74	26	A (81) 65	11
			60	40	B (95) 65	20
f	Me	Me	86	14	A (95) 80	11
			84	16	B (92) 75	14
g	Me	Ph	46	54	A (69) 28	36
			85	15[d]	B (89) 73	12
h	H	H		[e]	C –	85(94)
i	H	Me		[e]	C –	77(92)
j	H	Ph		[e]	C –	75(96)

[a] The ratio of regioisomers was estimated by GC-MS of the crude reaction mixture; [b]yield after purification (yield of the crude product is given in parentheses; for details, see Experimental); [c]the ratio of regioisomers was estimated by ^{1}H NMR; [d]the reaction was carried out at room temperature; [e]the ratio could not be determined exactly due to exchange process (see text)



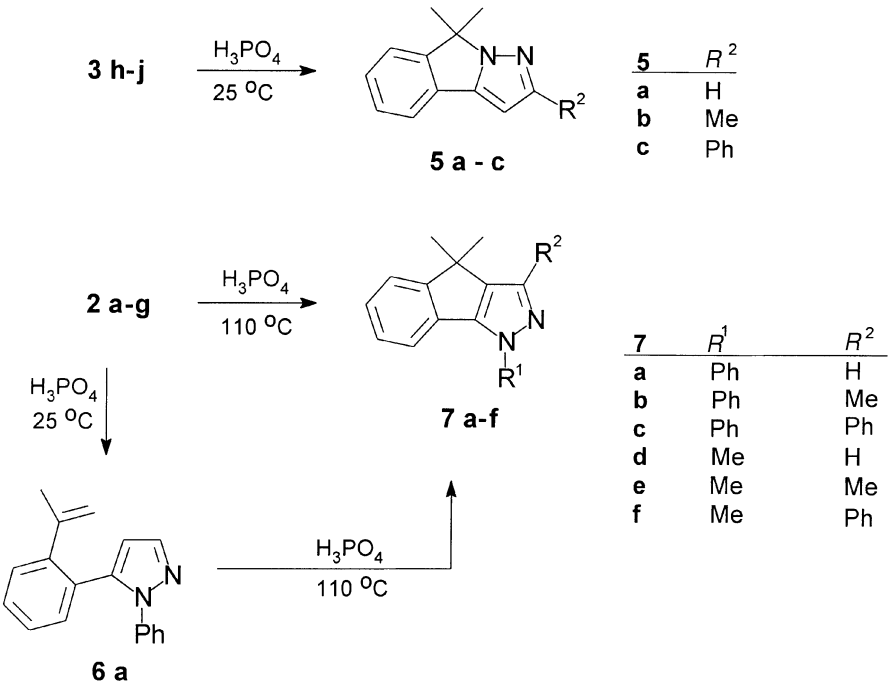
Scheme 1

afforded N-methyl substituted pyrazoles **2** and **3** with relatively low regioselectivity. As compared to **1a–b**, the regioselectivity of the reaction of 1-benzoylmethylene derivative (**1c**) with hydrazine derivatives was lower in all cases. The extremely low regioselectivity in the reaction of **1c** with methylhydrazine (Table 1, **2g**:**3g** = 46:54) could be improved. Hydrazine hydrate gave **3h–j** as dominant regioisomers.

Only regioisomers above 5% were isolated, and their structures were studied using spectroscopic methods. Pure pyrazoles **2a–j** are easily crystallizable compounds. In order to separate two isomeric pyrazoles **2** and **3**, an initial enrichment of the minor isomer by fractional crystallization of **2** was performed.

In the electrophilic substitution of the pyrazole ring, the attack of an electrophile usually takes place at C-4. However, in N-phenyl substituted derivatives the pyrazole ring behaves like a *pseudo*-halogen *ortho-para* directing substituent; thus, the *ortho* position of the phenyl ring could compete with position 4 of the pyrazole. Moreover, in the NH-pyrazole series the pyridine-like nitrogen atom can act as a nucleophilic site yielding N-substituted derivatives.

Among the reagents studied in the intramolecular alkylation of **2** and **3**, orthophosphoric acid was found to be the most convenient one. Stirring of



Scheme 2

pyrazoles **3h–j** in orthophosphoric acid at room temperature caused substitution of the hydroxy group by the nitrogen atom of pyrazole providing 8,8-dimethylpyrazolo[5,1-*a*]isoindoles (**5a–c**) (Scheme 2), whereas under the same reaction conditions pyrazoles **2a–g** underwent dehydration to the corresponding alkenes as documented for derivative **6a** (Scheme 2). Heating **2a–g** (or the corresponding alkenes) in orthophosphoric acid at 110°C gave smooth intramolecular electrophilic substitution at C-4 of the pyrazole ring, affording 4,4-dimethyl-1,4-dihydroindeno[1,2-*c*]pyrazoles **7a–f** after 2–3 hours (Scheme 2). In the case of **7a–c**, no substitution in the *ortho* position of the N-phenyl ring was observed. The N-substituted pyrazoles **3c**,**e–g** were found to be sensitive to acids and suffer destruction in the presence of phosphoric acid. Products **5**, **6**, and **7** were formed in high yields and good purity according to ^{1}H NMR spectra and GC-MS analysis.

The structures of pyrazoles **2**, **3**, **6**, and **7** were elucidated using 1D NMR (^{1}H, ^{13}C, ^{13}C-DEPT), 2D NMR (COSY, COLOC), and mass spectrometry. Additionally, ^{15}N NMR spectra were recorded for **2**, **3**, **5**, and **7**. ^{15}N NMR chemical shifts were comparable with data reported for different pyrazoles [8], thus corroborating the assignment. N-Methyl (**2e–g**, **3e–g**) and N-phenyl (**2c**, **3c**) regioisomeric pyrazoles were differentiated by means of their ^{1}H NMR spectra. The chemical shift of the OH proton served as the main identification criterion in these cases. In the regioisomer **2** this proton appears at higher field ($\delta = 1.65$–2.32 ppm), whereas in **3** it is shifted to lower field ($\delta = 6.50$–7.50 ppm) due to an intramolecular OH$\cdots$N hydrogen bond. The equivalence of the ^{1}H and ^{13}C NMR resonance position of the two CH_3 substituents of the α-hydroxyisopropyl moiety

in **3** gives further evidence for the existence of an OH···N-2 hydrogen bond. The absence of the OH···N-2 hydrogen bond in **2** allows free rotation of the α-hydroxyisopropyl fragment, but it is slow with respect to the NMR time scale, causing nonequivalence of the resonance position of the two CH_3 groups. The intensity of the molecular ion in the mass spectra can also be used as a criterion to differentiate between **3c,e–g** (relative intensity 0.5–1%) and **2a–g** (relative intensity > 25%).

The NH-pyrazoles **3h–j** exist in solution in a fast proceeding equilibrium of annular tautomers [9] as indicated by broadening of some signals in the ^1H, ^{13}C, and ^{15}N NMR spectra. Although we were not able to establish the ratio of regioisomers accurately, the chemical shifts of the OH proton ($\delta_{OH} = 5.81$–8.68 ppm, giving evidence of the week intramolecular hydrogen bond) and the value of $J_{4,5} = 2.3$ Hz for compound **3h**, which is more similar to $J_{4,5}$ of its N-methyl fixed analogue **3e** (2.2 Hz) than to $J_{4,5}$ of the isomer **2e** (1.8 Hz) [10], suggested that the regioisomers **3h–j** highly dominated.

Concerning the mechanism of the formation of **2** it could be assumed that the reaction starts with the condensation yielding the corresponding hydrazone (*e.g.* **4**, Scheme 1, path a). Subsequent attack of the second amino group of the hydrazine moiety at the second electrophilic site results in a spiro adduct which finally is opened. This proposed mechanism was confirmed for *p*-nitrophenyhydrazine, where the *p*-nitrophenylhydrazone (**4**) could be isolated. Reflux of **4** in pyridine in the presence of hydrochloric acid then yielded **2d**.

In the case of methylhydrazine, the lower regioselectivity as compared to aromatic hydrazines can be explained by competition of the stronger nucleophilic methyl substituted nitrogen atom relative with the NH_2 group for the nucleophilic attack at the carbonyl or the enol ether carbon atom (Scheme 1, path b). Subsequent elimination of water provides the corresponding pyrazoles **2** (Scheme 1, path c) and **3** (Scheme 1, path d).

In conclusion, the formation of the fused parazoles **5a–c** and **7a–f** by intramolecular alkylation of the pyrazole ring represents a new and suitable route to these ring systems. A pyrazole similar to **5a–c**, but with an 8-unsubstituted 8*H*-pyrazolo[5,1-*a*]isoindole structure, has been obtained from 5-(2-bromomethylphenyl)-3-phenyl-1*H*-pyrazole by treatment with sodium in boiling ethanol [11] or as the by-product in the formation of 2-amino-2,3-dihydro-1*H*-isoindol-1-one [12]. According to our knowledge there is only one incompletely described example of the synthesis of 4,4-dimethyl-1,4-dihydroindeno[1,2-*c*]pyrazole derivatives [13], whereas systems unsubstituted at position C-4 are easily obtained from 2-acyl-1,3-indandiones [14,15].

Experimental

Melting points were determined on a Boetius hot stage apparatus and are uncorrected. ^1H, ^{13}C, and ^{15}N NMR spectroscopic measurements were performed on a Bruker DPX 400 apparatus. *TMS* was used as internal reference for ^1H and ^{13}C NMR spactra. ^{15}N NMR chemical shifts were referenced to CH_3NO_2 at 300 K. Mass spectra (70 eV) were recorded with a HP 6890 (Hewlett-Packard) GCMS spectrometer equipped with a mass detector HP 5973. All compounds gave satisfactory elemental analyses (C,H). Silica gel (0.04–0.063 mm, Merck) was used for preparative column chromatog-

raphy. In some cases, the yield of crude products is given in parentheses. The starting 1-acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofurans (**1a–c**) were prepared from diethyl phthalate as described earlier [16].

5(3)-(2-(α-Hydroxyisopropyl)-phenyl)-pyrazoles **2a–g**, **3c**, **3e–g**; *General procedure*

Procedure A. To a solution of 2.15 mmol 1-acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofuran (**1a–c**) in 3.5 cm^3 dry pyridine, 2.17 mmol of the appropriate hydrazine hydrochloride or a mixture of 2.17 mmol hydrazine derivative and 2.17 mmol pyridine hydrochloride were added rapidly at ambient temperature. The mixture was refluxed for 1.5–2 h, cooled, and poured into 50 cm^3 cold H_2O. The resulting solid or oil was separated, washed with H_2O and hexane, and dried. Crystallization from a mixture of H_2O:ethanol = 1:1 yielded isomers **2a–g** as white crystals in most cases. In the case of **2c**, **3c**, **2e–g**, and **3e–g** the mother liquors contained mixtures of isomers **2** and **3**. The solvent was evaporated, and the residue was dried by distillation with dry benzene *in vacuo*. The residue was chromatographed on silica gel using *n*-hexane:ethyl acetate = 7:3 as eluent.

N-Methyl-3(5)-(2-(α-hydroxyisopropyl)-phenyl)-pyrazoles **2e–g**, **3e–g**; *General procedure*

Procedure B. 2.15 mmol of 1-acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofuran (**1a–c**) were dissolved in 1.35 cm^3 (25.35 mmol) of methyl hydrazine, and a few drops of concentrated HCl added. After reflux (1.5–2 h), the excess of methyl hydrazine was evaporated *in vacuo*. The mixture of **2** and **3** was separated as described in procedure A.

3-(2-(α-Hydroxyisopropyl)-phenyl)-pyrazoles **3h–j**; *General procedure*

Procedure C. 2.15 mmol of 1-acylmethylene-3,3-dimethyl-1,3-dihydroisobenzofuran (**1a–c**) were dissolved in 1.25 cm^3 (25.75 mmol) of hydrazine monohydrate. After reflux (1.5–2 h), the excess of hydrazine monohydrate was evaporated *in vacuo*, and the residue was crystallized from a mixture of H_2O-ethanol yielding white crystals.

5-(2-(α-Hydroxyisopropyl)-phenyl)-1-phenylpyrazole (**2a**; $C_{18}H_{18}N_2O$)

Procedure A; yield: 76(92)%; m.p.: 112–114°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.37 (br s, $2CH_3$), 1.90 (s, OH), 6.40 (d, $J = 1.7$, 4-H), 7.10 (dd, $J = 1.4$, 7.6, 7-H), 7.12–7.23 (m, C_6H_5, 8-H, 4H), 7.30 –7.38 (m, C_6H_5, 9-H, 3-H), 7.53 (dd, $J = 0.9$, 8.1, 10-H), 7.70 (d, $J = 1.7$, 3-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 31.4 (12-CH_3), 32.9 (12-CH_3), 73.8 (C-12), 108.8 (C-4), 123.9, 126.6 128.6, 140.3 (C_6H_5), 126.3 (C-8), 126.8 (C-10), 127.9 (C-6), 129.1 (C-9), 132.9 (C-7), 139.7 (C-3), 143.6 (C-5), 148.1 (C-11) ppm; ^{15}N NMR (*DMSO*-d_6, δ, 40 MHz): −76.6 (N-2), −163.4 (N-1) ppm; MS (70 eV): $m/z = 278$ (43, M^+), 263 (100), 245 (15), 219 (15).

5-(2-(α-Hydroxyisopropyl)-phenyl)-3-methyl-1-phenylpyrazole (**2b**; $C_{19}H_{20}N_2O$)

Procedure A; yield: 65(94)%; m.p.: 129–130°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.48 (br s, $2CH_3$), 2.00 (s, OH), 2.38 (s, CH_3), 6.21 (s, 4-H), 7.05–7.22 (m, C_6H_5, 7-H, 8-H, 5H), 7.26 – 7.31 (m, C_6H_5, 2H), 7.33 (ddd, $J = 1.6$, 7.3, 8.1, 9-H), 7.51 (dd, $J = 0.9$, 8.1, 10-H) ppm; ^{13}C NMR ($CDCl_3$, δ 100 MHz): 13.6 (3-CH_3), 31.4 (12-CH_3), 32.9 (12-CH_3), 73.8 (C-12), 108.8 (C-4), 123.7, 126.3, 128.6, 140.3 (C_6H_5), 126.3 (C-8), 126.7 (C-10), 128.1 (C-6), 129.0 (C-9), 132.9 (C-7), 144.2 (C-5), 147.9 (C-3), 148.9 (C-11) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −82.7 (N-2), −168.0 (N-1) ppm; MS (70 eV): $m/z = 292$ (75, M^+), 277 (100), 273 (22), 259 (24), 233 (17), 217 (12), 182 (6), 165 (6), 115 (7), 91 (10), 77 (10).

5-(2-(α-Hydroxyisopropyl)-phenyl)-1,3-diphenylpyrazole (**2c**; $C_{24}H_{22}N_2O{*}H_2O$)

Procedure A; yield: 65%; m.p.: 116–117°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.20 (t, $J = 7.0$, CH_3CH_2OH), 1.39 (br s, 12-CH_3), 1.42 (br s, 12-CH_3), 1.83 (br s, 2OH), 3.67 (q, $J = 7.0$, CH_3CH_2OH), 6.74 (s, 4-H), 7.15–7.45 (m, $2C_6H_5$, 7-H, 8-H, 9-H, 11H), 7.54 (d, $J = 8.0$, 10-H), 7.94 (d, $J = 7.2$, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 13.4 (CH_3), 31.5 (12-CH_3), 32.9 (12-CH_3), 58.3 (CH_2OH), 73.8 (C-12), 106.2 (C-4), 123.9, 125.8, 126.7 127.8, 128.6, 128.7, 132.9, 140.3 ($2C_6H_5$), 126.4 (C-8), 126.8 (C-10), 127.8 (C-6), 129.2 (C-9), 132.9 (C-7), 145.1 (C-5), 148.0 (C-11), 151.3 (C-3) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −85.2 (N-2), −164.3 (N-1) ppm; MS (70 eV): $m/z = 354$ (100, M^+), 339 (85), 336 (44), 335 (44), 321 (36), 295 (14), 244 (17), 217 (15), 91 (12), 77 (13).

5-(2-(α-Hydroxyisopropyl)-phenyl)-1-(4-nitrophenyl)pyrazole (**2d**; $C_{18}H_{17}N_3O_3$)

Procedure A; yield 68(90)%; m.p.: 137–139°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.43 (br s, 12-CH_3), 1.45 (br s, 12-CH_3), 1.65 (s, OH), 6.46 (d, $J = 1.7$, 4-H), 7.09 (dd, $J = 1.3$, 7.6, 7-H), 7.25 (td, $J = 1.2$, 7.5, 8-H), 7.44 (ddd, $J = 1.5$, 7.4, 8.0, 9-H), 7.51 (d, $J = 9.3$, 4-$NO_2C_6H_4$, 2H), 7.55 (dd, $J = 0.9$, 8.1, 10-H), 7.77 (d, $J = 1.7$, 3-H), 8.08 (d, $J = 9.3$, 4-$NO_2C_6H_4$, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 31.5 (12-CH_3), 33.3 (12-CH_3), 73.8 (C-12), 110.2 (C-4), 123.1, 124.3, 145.3, 145.3 (4-$NO_2C_6H_4$), 126.9 (C-8), 127.0 (C-10), 127.6 (C-6), 129.7 (C-9), 132.5 (C-7), 141.0 (C-3), 144.6 (C-5), 147.9 (C-11) ppm; ^{15}N NMR (*DMSO*-d_6, δ, 40 MHz): −11.5 (NO_2), −77.1 (N-2), −165.6 (N-1) ppm; MS (70 eV): $m/z = 323$ (25, M^+), 308 (100), 290 (5), 262 (21), 244 (5), 218 (9).

5-(2-(α-Hydroxyisopropyl)-phenyl)-1-methylpyrazole (**2e**; $C_{13}H_{16}N_2O$)

Procedure A: yield: 65%; procedure B: yield 65%; m.p.: 123–125°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.38 (br s, CH_3), 1.53 (br s, CH_3), 2.32 (br s, OH), 3.59 (s, 1-CH_3), 6.23 (d, $J = 1.8$, 4-H), 7.08 (dd, $J = 1.4$, 7.5, 7-H), 7.29 (td, $J = 1.3$, 7.5, 8-H), 7.43 (ddd, $J = 1.5$, 7.4, 8.1, 9-H), 7.50 (d, $J = 1.8$, 3-H), 7.70 (dd, $J = 1.0$, 8.1, 10-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 31.8 ($2CH_3$), 36.9 (1-CH_3), 73.3 (C-12), 106.9 (C-4), 126.2 (C-8), 126.5 (C-10), 127.8 (C-6), 129.3 (C-9), 132.2 (C-7), 138.1 (C-3), 143.5 (C-5), 148.5 (C-11) ppm; ^{15}N NMR (*DMSO*-d_6, δ, 40 MHz): −75.8 (N-2), −178.5 (N-1) ppm; MS (70 eV): $m/z = 216$ (39, M^+), 201 (100), 183 (21), 168 (12), 157 (12), 128 (7), 115 (10).

5-(2-(α-Hydroxyisopropyl)-phenyl)-1,3-dimethylpyrazole (**2f**; $C_{14}H_{18}N_2O$)

Procedure A: yield: 80%; procedure B: yield 75%; m.p.: 123–125°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.43 (br s, 12-CH_3), 1.52 (br s, 12-CH_3), 2.17 (br s, OH), 2.30 (s, 3-CH_3), 3.52 (s, 1-CH_3), 6.02 (s, 4-H), 7.08 (dd, $J = 1.3$, 7.6, 7-H), 7.28 (td, $J = 1.3$, 7.4, 8-H), 7.42 (ddd, $J = 1.5$, 7.4, 8.0, 9-H), 7.66 (dd, $J = 1.0$, 8.0, 10-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 13.5 (3-CH_3), 31.7 (12-CH_3), 31.9 (12-CH_3), 36.6 (1-CH_3), 73.4 (C-12), 106.5 (C-4), 126.1 (C-8), 126.5 (C-10), 128.0 (C-6), 129.2 (C-9), 132.2 (C-7), 144.2 (C-5), 147.4 (C-3), 148.4 (C-11) ppm; ^{15}N NMR (*DMSO*-d_6, δ, 40 MHz): −79.4 (N-2), −183.9 (N-1) ppm; MS (70 eV): $m/z = 230$ (70, M^+), 215 (100), 211 (15), 197 (32), 182 (10), 171 (12), 128 (10), 115 (9).

5-(2-(α-Hydroxyisopropyl)-phenyl)-1-methyl-3-phenylpyrazole (**2g**; $C_{19}H_{20}N_2O$)

Procedure A: yield: 28%; procedure B: yield 73%; m.p.: 101–103°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.44 (br s, 12-CH_3), 1.55 (br s, 12-CH_3), 2.06 (s, OH), 3.63 (s, 1-CH_3), 6.55 (s, 4-H), 7.15 (dd, $J = 1.2$, 7.5, 7-H), 7.25 – 7.50 (m, 8-H, 9-H, C_6H_5, 5H), 7.69 (d, $J = 8.0$, 10-H), 7.82 (d, $J = 7.3$, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 31.8 (12-CH_3), 32.0 (12-CH_3), 37.5 (1-CH_3), 73.5 (C-12), 104.0 (C-4), 125.5, 127.8, 128.6, 133.2 (C_6H_5), 126.2 (C-10), 126.6 (C-8), 128.6 (C-6), 129.4 (C-9), 132.2 (C-7), 145.0 (C-5), 148.4 (C-3), 150.1 (C-11) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz):

−85.5 (N-2), −180.4 (N-1) ppm; MS (70 eV): *m/z* = 292 (100, M^+), 277 (79), 273 (27), 259 (37), 233 (11), 131 (8), 104 (7), 77 (8).

3-(2-(α-Hydroxyisopropyl)-phenyl)-1,5-diphenylpyrazole (**3c**; $C_{24}H_{22}N_2O$)

Procedure A; yield: 14%; oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.59 (s, $2CH_3$), 6.69 (s, 4-H), 7.23–7.38 (m, $2C_6H_5$, OH, 8-H, 9-H, 13H), 7.59–7.63 (m, 7-H, 10-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 30.0 ($2CH_3$), 71.8 (C-12), 108.5 (C-4), 124.8, 127.7, 128.4, 128.6, 128.8, 129.0, 131.5, 139.3 ($2C_6H_5$), 126.3 (C-10), 127.0 (C-8), 128.7 (C-9), 129.8 (C-6), 132.1 (C-7), 144.3 (C-3), 146.1 (C-11), 154.4 (C-5) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −85.2 (N-2), −170.6 (N-1) ppm; MS (70 eV): *m/z* = 354 (0.5, M^+), 339 (100), 335 (29), 296 (12), 77 (10).

3-(2-(α-Hydroxyisopropyl)-phenyl)-1-methylpyrazole (**3e**; $C_{13}H_{16}N_2O$)

Procedure A: yield: 11%; procedure B: yield: 20%; oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.47 (s, $2CH_3$), 3.93 (s, 1-CH_3), 6.40 (d, *J* = 2.2, 4-H), 6.50 (br s, OH), 7.25–7.34 (m, 9-H, 10-H), 7.42 (d, *J* = 2.2, 5-H), 7.43 – 7.57 (m, 7-H, 8-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 29.8 ($2CH_3$), 38.9 (1-CH_3), 71.7 (C-12), 106.4 (C-4), 126.0 (C-8), 126.9 (C-10), 128.0 (C-9), 131.4 (C-5), 132.0 (C-7), 132.0 (C-6), 145.9 (C-11), 154.0 (C-3) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −86.4 (N-2), −183.7 (N-1) ppm; MS (70 eV): *m/z* = 216 (0.2, M^+), 202 (14), 201 (100), 197 (6), 183 (19), 168 (9), 159 (10), 158 (10), 157 (5), 115 (7), 93 (5).

3-(2-(α-Hydroxyisopropyl)-phenyl)-1,5-dimethylpyrazole (**3f**; $C_{14}H_{18}N_2O$)

Procedure A: yield: 11%; procedure B: yield: 14%; oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.48 (s, $2CH_3$), 2.28 (s, 5-CH_3), 3.75 (s, 1-CH_3), 6.16 (s, 4-H), 7.22 (br s, OH), 7.23–7.30 (m, 9-H, 10-H), 7.39–7.44 (m, 9-H), 7.51 – 7.56 (m, 10-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 10.8 (5-CH_3), 29.7 ($2CH_3$), 35.9 (1-CH_3), 71.5 (C-12), 105.8 (C-4), 125.8 (C-8), 126.7 (C-10), 127.6 (C-9), 131.7 (C-7), 132.2 (C-6), 139.8 (C-5), 145.7 (C-11), 152.3 (C-3) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −89.1 (N-2), −185.3 (N-1) ppm; MS (70 eV): *m/z* = 230 (1, M^+), 215 (100), 211 (10), 197 (10), 173 (10), 172 (9), 156 (5), 128 (4), 100 (6), 56 (5).

3-(2-(α-Hydroxyisopropyl)-phenyl)-1-methyl-5-phenylpyrazole (**3g**; $C_{19}H_{20}N_2O$)

Procedure A: yield: 36%; procedure B: yield: 12%; m.p.: 120–122°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.54 (s, $2CH_3$), 3.91 (s, 1-CH_3), 6.48 (s, 4-H), 7.29 (td, *J* = 1.6, 7.3, 8-H), 7.33 (td, *J* = 1.9, 7.3, 9-H), 7.41–7.53 (m, C_6H_5, 7-H, 6H), 7.45 (br s, OH), 7.58 (dd, *J* = 1.9, 7.3, 10-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 30.0 ($2CH_3$), 37.6 (1-CH_3), 71.8 (C-12), 106.5 (C-4), 126.1 (C-10), 126.9 (C-8), 128.1 (C-9), 128.7, 128.8, 128.9, 131.9 (C_6H_5), 129.9 (C-6), 132.0 (C-7), 145.1 (C-5), 146.0 (C-11), 153.1 (C-3) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −85.6 (N-2), −187.7 (N-1) ppm; MS (70 eV): *m/z* = 292 (0.5, M^+), 277 (100), 273 (17), 259 (7), 234 (13), 217 (6), 131 (8), 77 (5).

3-(2-(α-Hydroxyisopropyl)-phenyl)pyrazole (**3h**; $C_{12}H_{14}N_2O$)

Procedure C; yield: 85(94)%; m.p.: 158–159°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.50 (s, $2CH_3$), 6.45 (d, *J* = 2.3, 4-H), 7.28 – 7.35 (m, 9-H, 10-H), 7.49–7.58 (m, 7-H, 8-H), 7.57 (d, *J* = 2.3, 5-H), 7.94 (br s, OH), 12.39 (br s, NH) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 29.8 ($2CH_3$), 72.5 (C-12), 105.5 (C-4), 126.1 (C-8), 127.3 (C-10), 128.1 (C-9), 131.2 (br, C-5), 131.8 (C-6), 132.3 (C-7), 145.0 (C-11), 151.9 (br, C-3) ppm; ^{15}N NMR (*DMSO*-d_6, δ,40 MHz): −91.3 (br, N-2), −175.6 (br, N-1) ppm; MS (70 eV): *m/z* = 202 (16, M^+), 187 (72), 169 (100), 144 (9), 128 (8), 115 (23).

3-(2-(α-Hydroxyisopropyl)-phenyl)-5-methylpyrazole (**3i**; $C_{13}H_{16}N_2O$)

Procedure C; yield: 77(92)%; m.p.: 152–154°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.53 (s, $2CH_3$), 2.48 (s, 5-CH_3), 6.19 (s, 4-H), 7.24–7.34 (m, 9-H, 10-H), 7.47–7.58 (m, 7-H, 8-H), 8.68 (br s, OH), 12,12 (br s, NH) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 11.0 (5-CH_3), 29.7 ($2CH_3$), 72.4 (C-12), 104.6 (C-4), 126.0 (C-8), 127.1 (C-10), 127.8 (C-9), 132.0 (C-7), 132.3 (C-6), 141.0 (C-5), 145.1 (C-11), 153.0 (C-3) ppm; ^{15}N NMR (*DMSO*-d_6, δ; 40 MHz): −96.0 (br, N-2), −175.6 (br, N-1) ppm; MS (70 eV): $m/z = 216$ (11, M^+), 201 (46), 198 (20), 197 (19), 183 (100), 168 (11), 158 (10), 128 (9), 115 (15).

3-(2-(α-Hydroxyisopropyl)-phenyl)-5-phenylpyrazole (**3j**; $C_{18}H_{18}N_2O$)

Procedure C; yield: 75(96)%; m.p.: 154–157°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.59 (s, $2CH_3$), 5.81 (br s, OH, NH), 6.76 (s, 4-H), 7.35–7.38 (m, 9-H, 10-H, C_6H_5, 3H), 7.44 (t, $J = 7.7$, C_6H_5, 2H), 7.60 – 7.64 (m, 7-H, 8-H), 7.79 (d, $J = 7.2$, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 29.8 ($2CH_3$), 72.9 (C-12), 102.7 (C-4), 125.7, 128.4, 128.9, 131.0 (C_6H_5), 126.1 (C-8), 127.4 (C-10), 128.1 (C-9), 131.7 (C-6), 132.1 (C-7), 144.8 (C-5), 145.8 (br, C-11), 152.6 (br, C-3) ppm; ^{15}N NMR: no signals visible due to fast exchange; MS (70 eV): $m/z = 278$ (11, M^+), 263 (43) 260 (31), 259 (16), 245 (100), 220 (9), 115 (8), 77 (7).

8,8-Dimethylpyrazolo[5,1-a]isoindoles **5a–c**; *5-(2-(Isopropenyl)-phenyl)pyrazole* **6a**; *General procedure*

1.44 mmol of **3h–j** or **2a** was stirred in 6 cm^3 of orthophosphoric acid at room temperature for 2–3 h. After pouring into 50 cm^3 of cold H_2O, the suspension was cooled in a H_2O-ice bath, and the acid was carefully neutralized by treatment with KOH (pellets). The mixture was extracted twice with 50 cm^3 ethyl acetate. The combined organic layers were washed with water, separated, dried over $MgSO_4$, filtered through a 2 cm layer of Celite, and evaporated *in vacuo*. The crude products **5a–c** and **6a** were purified by column chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (7:3) as eluent.

8,8-Dimethylpyrazolo[5,1-a]isoindole (**5a**; $C_{12}H_{12}N_2$)

Yield: 77(89)%; m.p.: 54–56°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.69 (s, $2CH_3$), 6.35 (d, $J = 1.9$, 3-H), 7.28–7.39 (m, 4-H, 5-H, 6-H), 7.52–7.58 (m, 7-H),7.65 (d, $J = 1.9$, 2-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 26.7 ($2CH_3$), 65.1 (C-8), 96.5 (C-3), 120.5 (C-4), 121.7 (C-7), 127.3 (C-5), 128.1 (C-6), 128.9 (C-11), 142.8 (C-10), 143.2 (C-2), 151.3 (C-12) ppm; ^{15}N NMR (*DMSO*-d_6, δ, 40 MHz): −90.1 (N-1), −139.8 (N-9) ppm; MS (70 eV): $m/z = 184$ (46, M^+), 169 (100), 128 (8), 115 (18).

2,8,8-Trimethylpyrazolo[5,1-a]isoindoles (**5b**; $C_{13}H_{14}N_2$)

Yield: 84(96)%; oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.67 (s, $2CH_3$), 2.40 (s, 2-CH_3), 6.14 (s, 3-H), 7.27–7.37 (m, 4-H, 5-H, 6-H), 7.50–7.52 (m, 7-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 14.5 (2-CH_3), 26.8 ($2CH_3$), 64.9 (C-8), 96.0 (C-3), 120.3 (C-4), 121.6 (C-7), 127.1 (C-5), 128.0 (C-6), 129.1 (C-11), 143.6 (C-10), 151.2 (C-12), 152.8 (C-2) ppm; ^{15}N NMR (*DMSO*-d_6, δ, 40 MHz): −93.8 (N-1), −145.3 (N-9) ppm; MS (70 eV): $m/z = 198$ (44, M^+), 183 (100), 168 (13), 115 (14).

8,8-Dimethyl-2-phenylpyrazolo[5,1-a]isoindole (**5c**; $C_{18}H_{16}N_2$)

Yield: 88(96)%; oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.74 (s, $2CH_3$), 6.66 (s, 3-H), 7.28–7.45 (m, C_6H_5, 4-H, 5-H, 6-H, 6H), 7.58–7.62 (m, 7-H), 7.86 – 7.91 (m, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ,

100 MHz): 26.8 ($2CH_3$), 65.5 (C-8), 93.6 (C-3), 120.5 (C-4), 121.6 (C-7), 127.4 (C-5), 128.1 (C-6), 125.7, 127.5, 128.6, 134.3 (C_6H_5), 128.9 (C-11), 144.0 (C-10), 151.1 (C-12), 155.7 (C-2) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −99.7 (N-1), −142.2 (N-9) ppm; MS (70 eV): $m/z = 260$ (54, M^+), 245 (100), 169 (5), 115 (7), 77 (7).

5-(2-Isopropenyl)phenyl-1-phenylpyrazole (**6a**; $C_{18}H_{16}N_2$)

Yield: 57(63)%; oil; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.45 (br s, 12-CH_3), 4.46 (br d, $J = 0.8$, =C*H*H), 4.80 (br t, $J = 1.4$, =CH*H*), 6.46 (d, $J = 1.7$, 4-H), 7.13–7.35 (m, C_6H_5, 7-H, 8-H, 9-H, 10-H, 9H), 7.70 (d, $J = 1.7$, 3-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 22.4 (12-CH_3), 109.1 (C-4), 116.2 (=CH_2), 124.1, 127.1, 128.6, 140.3 (C_6H_5), 126.6 (C-8), 128.4 (C-10), 128.6 (C-6), 128.8 (C-9), 130.8 (C-7), 140.0 (C-3), 142.2 (C-12), 143.2 (C-5), 143.9 (C-11) ppm; MS (70 eV): $m/z = 260$ (76, M^+), 259 (85), 245 (100), 232 (12), 217 (25), 168 (12), 167 (11), 141 (9), 128 (12), 115 (15), 77 (15).

4,4-Dimethyl-1,4-dihydroindeno[1,2-c]pyrazoles **7a–f**; *General procedure*

The procedure is exactly the same as described for the synthesis of **5a–c** and **6a** except that the reaction was conducted at 110°C. The crude products **7a,b,d,f** were purified by column chromatography on silica gel with a mixture of *n*-hexane and ethyl acetate (7:3) as eluent. Compounds **7c,e** were purified by crystallization from a mixture of *n*-hexane and ethyl acetate.

4,4-Dimethyl-1-phenyl-1,4-dihydroindeno[1,2-c]pyrazole (**7a**; $C_{18}H_{16}N_2$)

Yield: 75(82)%; oil; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.53 (s, $2CH_3$), 7.21 (td, $J = 1.2$, 7.5, 7-H), 7.27 (td, $J = 1.2$, 7.5, 6-H), 7.38–7.46 (m, 5-H, 8-H, C_6H_5, 3H), 7.54 (t, $J = 8.2$, C_6H_5, 2H), 7.61 (s, 3-H), 7.73 (br d, $J =$ ca. 8.2, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 26.7 ($2CH_3$), 41.2 (C-4), 119.4 (C-8), 123.1, 127.5, 129.3, 140.2 (C_6H_5), 123.4 (C-5), 126.6 (C-7), 126.9 (C-6), 130.0 (C-8a), 133.6 (C-3), 139.6 (C-3a), 144.9 (C-8b), 159.7 (C-4a) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −67.4 (N-2), −178.1 (N-1) ppm; MS (70 eV): $m/z = 260$ (55, M^+), 245 (100), 228 (7), 217 (11), 77 (9).

3,4,4-Trimethyl-1-phenyl-1,4-dihydroindeno[1,2-c]pyrazole (**7b**; $C_{19}H_{18}N_2$)

Yield: 79(99)%; oil; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.54 (s, $2CH_3$), 2.43 (s, 3-CH_3), 7.20 (td, $J = 1.2$, 7.5, 6-H), 7.26 (td, $J = 1.2$, 7.4, 7-H), 7.33–7.45 (m, 5-H, 8-H, C_6H_5, 3H), 7.51 (t, $J = 8.2$, C_6H_5, 2H), 7.70 (br d, $J = 8.2$, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 12.4 (3-CH_3), 25.5 ($2CH_3$), 41.2 (C-4), 119.4 (C-8), 122.9, 127.1, 129.3, 140.2 (C_6H_5), 123.3 (C-5), 126.6 (C-6), 126.7 (C-7), 130.2 (C-8a), 136.8 (C-3a), 143.5 (C-3), 145.6 (C-8b), 159.7 (C-4a) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz); −69.3 (N-2), −183.5 (N-1) ppm; MS (70 eV): $m/z = 274$ (49, M^+), 259 (100), 244 (8), 217 (23), 77 (7).

4,4-Dimethyl-1,3-diphenyl-1,4-dihydroindeno[1,2-c]pyrazole (**7c**; $C_{24}H_{20}N_2$)

Yield: 45(78)%; m.p.: 151–153°C; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.66 (s, $2CH_3$), 7.21 (td, $J = 0.8$, 7.5, 7-H), 7.28 (td, $J = 0.9$, 7.5, 6-H), 7.36 (t, $J = 7.4$, C_6H_5), 7.38 – 7.50 (m, 5-H, 8-H, C_6H_5, 5H), 7.55 (t, $J = 7.6$, C_6H_5, 2H), 7.79 (d, $J = 7.5$, C_6H_5, 2H), 7.97 (d, $J = 8.4$, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 25.1 ($2CH_3$), 42.2 (C-4), 119.3 (C-8), 123.3 (C-5), 123.5, 127.5, 127.6, 127.8, 128.5, 129.3, 133.5, 140.1, ($2C_6H_5$), 126.6 (C-7), 127.0 (C-6), 129.6 (C-8a), 135.7 (C-3a), 146.7 (C-8b), 147.1 (C-3), 160.0 (C-4a) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −70.55 (N-2), −180.6 (N-1) ppm; MS (70 eV): $m/z = 336$ (69, M^+), 321 (100), 305 (48), 243 (6), 229 (6), 217 (15), 77 (10).

1,4,4-Trimethyl-1,4-dihydroindeno[1,2-c]pyrazole (**7d**; $C_{13}H_{14}N_2$)

Yield: 85(98)%; oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.46 (s, $2CH_3$), 4.10 (s, 1-CH_3), 7.24–7.32 (m, 6-H, 7-H), 7.35 (s, 3-H), 7.39 (dm, J = ca. 7.3, 5-H), 7.46 (dm, J = ca. 7.3, 8-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 26.8 ($2CH_3$), 37.5 (1-CH_3), 41.4 (C-4), 118.3 (C-8), 123.5 (C-5), 126.6 (C-7), 126.7 (C-6), 130.0 (C-8a), 131.3 (C-3), 137.7 (C-3a), 145.8 (C-8b), 159.5 (C-4a) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −68.1 (N-2), −198.1 (N-1) ppm; MS (70 eV): m/z = 198 (42, M^+), 183 (100), 168 (16), 140 (7), 127 (6).

1,3,4,4-Tetramethyl-1,4-dihydroindeno[1,2-c]pyrazole (**7e**; $C_{14}H_{16}N_2$)

Yield: 79(99)%; m.p.: 85–88°C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.47 (s, $2CH_3$), 2.32 (s, 3-CH_3), 4.02 (s, 1-CH_3), 7.27 (td, J = 1.3, 7.4, 7-H), 7.28 (td, J = 1.4, 7.4, 6-H), 7.37 (dm, J = ca. 7.3, 5-H), 7.43 (dm, J = ca. 7.3, 1H, 8-H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 12.3 (3-CH_3), 25.6 ($2CH_3$), 37.1 (1-CH_3), 41.3 (C-4), 118.4 (C-8), 123.4 (C-5), 126.4 (C-7), 126.7 (C-6), 130.2 (C-8a), 134.6 (C-3a), 141.1 (C-3), 146.5 (C-8b), 159.4 (C-4a) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): 71.6 (N-2), −204.3 (N-1) ppm; MS (70 eV): m/z = 212 (30, M^+), 197 (100), 182 (9), 140 (4), 128 (5).

1,4,4-Trimethyl-3-phenyl-1,4-dihydroindeno[1,2-c]pyrazole (**7f**; $C_{19}H_{18}N_2$)

Yield: 77(83)%; oil; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.49 (s, $2CH_3$), 4.01 (s, 1-CH_3), 7.15–7.39 (m, 5-H, 6-H, 7-H, 8-H, C_6H_5, 7H), 7.77 (d, J = 7.8, C_6H_5, 2H) ppm; ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 25.1 ($2CH_3$), 36.5 (1-CH_3), 41.3 (C-4), 117.2 (C-8), 122.4 (C-5), 125.6, 125.7 (C-6, C-7), 126.0, 126.3, 127.5, 132.7 (C_6H_5), 128.5 (C-8a), 132.5 (C-3a), 144.0 (C-3), 146.6 (C-8b), 158.6 (C-4a) ppm; ^{15}N NMR ($CDCl_3$, δ, 40 MHz): −73.4 (N-2), −200.1 (N-1) ppm; MS (70 eV): m/z = 274 (61, M^+), 259 (100), 230 (4), 156 (5), 127 (4), 77 (4).

Acknowledgments

The author thanks Dr. *Z. Wichert-Tur* for the initiation of this work and Prof. *J. Liebscher* from Humboldt University, Berlin, for helpful discussions and assistance with the preparation of the manuscript.

References

[1] Jones BG, Branch SK, Thompson AS, Threadgill, MD (1996) J Chem Soc Perkin Trans 1, 2685
[2] Walizei GH, Breitmaier E (1989) Synthesis **4**: 337
[3] Mühmel G, Hanke R, Breitmaier E (1982) Synthesis **6**: 673
[4] Karakhanov RA, Vartanyan MM, Solov'eva TYu, Zefirova VA (1984) Khim Geterotsikl Soedin **1**: 133
[5] Pätzel M, Liebscher J (1995) Synthesis **8**: 879
[6] Wichert – Tur Z (1993) Polish J Chem **67**: 1595
[7] Elguero J (1984) In: Potts KT (ed) Katritzky and Rees Comprehensive Heterocyclic Chemistry, vol 5, part 4A. Pergamon Press, Oxford, p 278
[8] Claramunt RM, Sanz D, Lopez C, Jimenez JA, Jimeno ML, Elguero J, Fruchier A (1997) Magn Reson Chem **35**: 35
[9] Elguero J (1984) In: Potts KT (ed) Katritzky and Rees Comprehensive Heterocyclic Chemistry, vol 5, part 4A. Pergamon Press, Oxford, p 190
[10] Elguero J (1984) In: Potts KT (ed) Katritzky and Rees Comprehensive Heterocyclic Chemistry, vol 5, part 4A. Pergamon Press, Oxford, p 182

[11] Doria G, Isetta AM, Ferreccio R, Ferrari M, Fornasiero MC (1991) Farmaco **46**: 843
[12] Toja E, Omodei-sale A, Nathansohn G (1979) Tetrahedron Lett **31**: 2921
[13] Kerbal A, Verbel J, Cerutti E, Laude B (1989) J Chem Soc Chem Commun **10**: 632
[14] Braun R, Mosher WA (1958) J Am Chem Soc **80**: 4919
[15] Hamilton RW (1976) J Heterocycl Chem **13**: 545
[16] Wichert-Tur Z (1988) Polish J Chem **62**: 715

Received November 4, 1999. Accepted (revised) December 3, 1999