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AN EASY METHOD FOR THE *N*-ALKYLATION OF AMIDES, CARBAMATES, UREAS AND AZOLES. REACTIVITY OF 4-CHLOROMETHYLPYRAZOLES WITH WEAK NUCLEOPHILES UNDER NEUTRAL CONDITIONS

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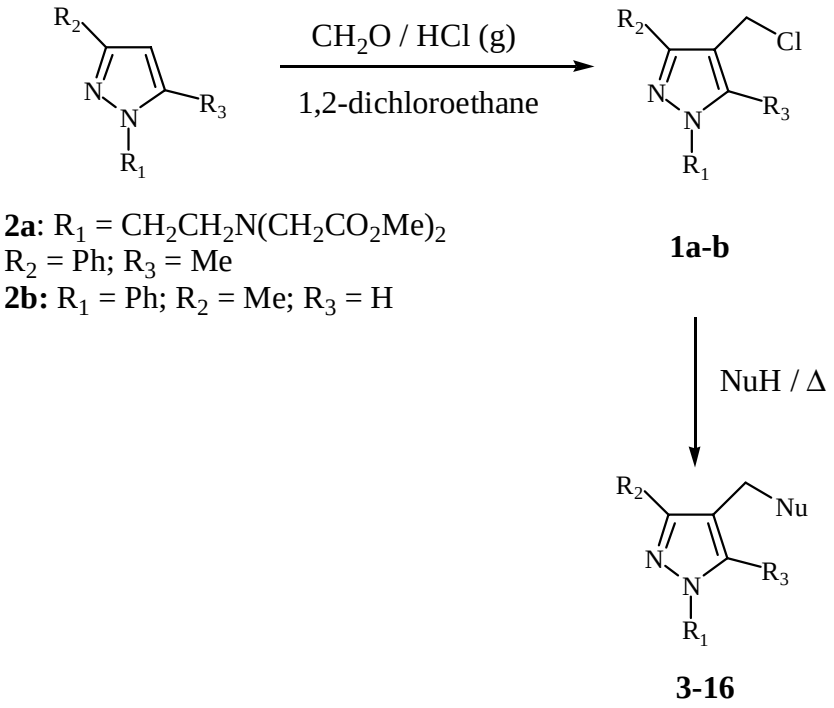
Abstract – 4-Chloromethylpyrazoles are shown to react readily with amides, carbamates, ureas and azoles under neutral conditions giving the corresponding *N*-monoalkylated derivatives with moderate yields. Alkylation of alcohols and thiols occurs under the same conditions. The procedure described may provide a convenient and easy method for the introduction of a 4-pyrazolylmethyl group into molecules containing functional groups with weak nucleophilic character.

N-Alkylation of amides is known to be a difficult process due to their low nucleophilic character.[1] Nevertheless, these reactions have been acomplished using different alkylating agents such as, electrophilic alkenes,[2] alcohols,[3] aldehydes or ketones[4] and alkyl halides.[5] Generally, the *N*-alkylated amides are obtained treating the starting amide with a strong base in an inert solvent followed by reaction with alkyl halide. However, under neutral conditions the direct alkylation using alkyl halides rarely leads exclusively to *N*-alkylated products. Instead, a mixture of both *O*- and *N*-alkylated isomers is normally isolated. Only at high temperatures the corresponding *N*-alkylated amides are obtained. In this work we report a convenient procedure for the alkylation of aliphatic and aromatic amides which results exclusively in the *N*-alkylation products. The method uses 4-chloromethylpyrazoles as alkylating agents.

Chloromethyl derivatives (**1a-b**) were synthesized by reaction of the corresponding pyrazoles (**2a-b**) with paraformaldehyde (Scheme 1).[6] Compound (**2a**) was obtained from 3-phenyl-5-methylpyrazole[7] using methods previously described by our laboratory.[8] Pyrazole (**2b**) is a commercial compound.



Scheme 1

Table 1. Results obtained in the reaction of 4-chloromethylpyrazoles (**1a-b**) with amides, carbamates, ureas, azoles, alcohols and thiols.

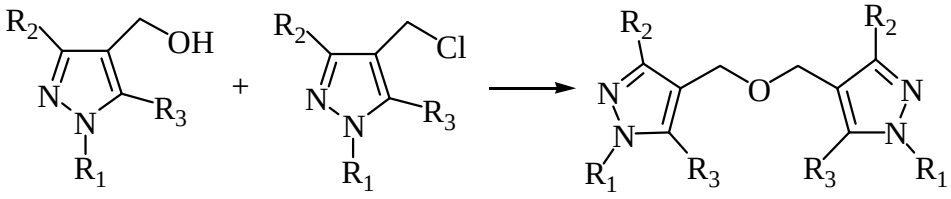
R-Cl	Nucleophile	R-Nu	Yield %	R-Cl	Nucleophile	R-Nu	Yield %
1a	Propionamide	**3**	42 [a]	**1b**	Pyrazole	**11**	90 [a]
1a	Benzamide	**4**	38 [a]	**1b**	4(5)-Nitroimidazole	**12**	27(3)[a,d]
1a	*t*-Bu carbamate	**5**	33 [a]	**1a**	Ethanol	**13**	52[b]
1b	Propionamide	**6**	39 [a]	**1a**	Benzyl alcohol	**14**	58[b]
1b	Benzamide	**7**	42 [a]	**1a**	1-Propanethiol	**15**	69 [a]
1b	Phenylurea	**8**	39 [a]	**1a**	Benzyl mercaptan	**16**	55 [a]
1b	Ethylurea	**9**	37 (19)[a, c]	**1a**	Ethylene glycol	**17a**	40[b]
1b	Imidazole	**10**	41 [a]	**1a**	Thioethylene glycol	**17b**	56[a]

All compounds were purified by column chromatography on silica gel and the yields are shown in isolated product.
[a] In DMF at 80 °C for 2 h.
[b] In 1,2-dichloroethane at 80 °C for 2 h.
[c] Yield of 1-ethyl-1-(3-methyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)urea (**9b**) in parenthesis.
[d] Yield of the minor 3-Methyl-4-(5-nitro-imidazol-1-ylmethyl)-1-phenyl-1*H*-pyrazole in parenthesis.

The results of the reaction of **1a** with propionamide and benzamide under neutral conditions are shown in Table 1. Interestingly, the nucleophilic substitution yielded the corresponding monoalkylated amides (**3**) and (**4**). These compounds were characterized by spectroscopic and analytical methods.[9] The ^{1}H-NMR spectra of the isolated amides depicted two doublets (^3J = 4.5 Hz) at 4.37 and 4.58 ppm respectively, derived from the corresponding CH_2-NH groups. The protons of the NHCO group appeared as broad

singlets. Similarly, the reaction of **1a** with *tert*-butyl carbamate under the same conditions than those used for amides, yielded *N*-substituted carbamate (**5**).[10]

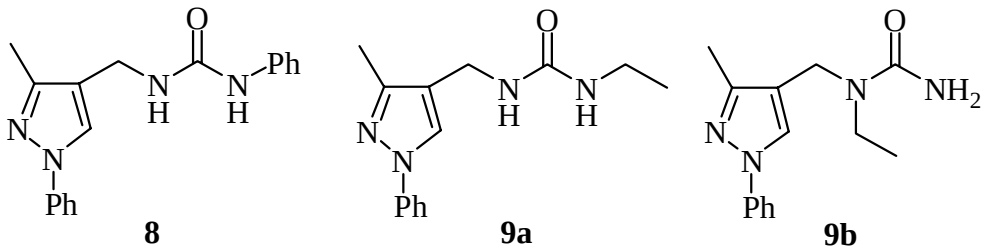
The 4-chloromethyl derivatives (**1a-b**) present higher reactivity than those pyrazoles containing the chloromethyl group in other positions.[11] Although literature on these compounds remains reduced, reactions with water,[12] cyanide ion[12,13] and organic anions have been reported.[12] In fact, the formation of the corresponding ethers was observed in some cases, due to the presence of traces of water in the reaction medium. These ethers were formed by coupling of the corresponding alcohol with the starting 4-chloromethylpyrazole (Scheme 2).



Scheme 2

We also investigated the nucleophilic substitution reactions of 4-chloromethylpyrazole (**1b**).[14] It should be noted here that **1b** contains a different *N*-substitution and no extra functional groups on the azole ring. The reaction of **1b** with propionamide and benzamide gave similar results to those of **1a**. The corresponding *N*-substituted products (**6**) and (**7**) were isolated with moderated yields (Table 1).[15]

4-Chloromethylpyrazole (**1b**) also reacted with phenyl and ethyl urea giving the corresponding *N*-(4-pyrazolylmethyl)ureas (**8**) and (**9**).[16] In the case of ethyl urea, both nitrogen atoms react with the chloromethylpyrazole (**1b**) yielding compounds (**9a**) and (**9b**) (Figure 1). ^{1}H-NMR and ^{13}C-NMR spectra of both compounds were very similar being particularly interesting the study of the IR spectra. While compound (**9a**) gave only one band at $\nu = 3308$ cm^{-1} corresponding to the NHCO group, compound (**9b**) presented two bands at $\nu = 3424$ cm^{-1} and $\nu = 3211$ cm^{-1} derived from the stretching of NH_2CO group. On the other hand, the ^{1}H-NMR spectrum of **8** depicted a doublet (^{3}J = 5.4 Hz) at 4.17 ppm corresponding to the CH_2-NHCO group. Even though the structure of compound (**9a**) is similar to that of compound (**8**)**,** the CH_2-NHCO coupling is not observed, probably as a consequence of the high rotation rate around the N-CO bond.

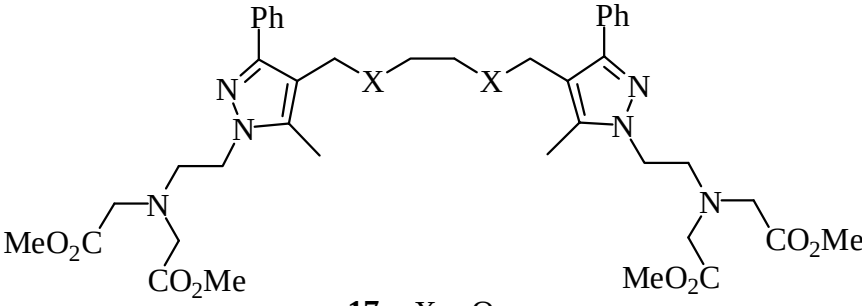


8 **9a** **9b**

Figure1

To further extend the scarce information on the reactivity of these chloromethylderivatives, we explored the reactions of 4-chloromethylpyrazoles (**1a-b**) with other nucleophiles as imidazole, 4-nitroimidazole and pyrazole (Scheme 1, Table 1). Frequently, *N*-alkylation of imidazoles and pyrazoles requires the use of an excess of azole in basic medium employing phase transfer conditions.[17] Here we have obtained the corresponding 1-(4-pyrazolylmethyl) azoles (**10-12**) using the alkylation conditions described in Table 1.[18] When 4(5)-nitroimidazole was employed, the *N*-substituted 4-nitroimidazole was isolated as major isomer, and the corresponding 5-nitroimidazole regioisomer was obtained with only a 3 % yield.

Considering that only two 4-alkoxymethylpyrazoles have been described previously,[12,19] we extended the reaction to alcohols and thiols. In all cases, the corresponding ethers and thioethers (**13-16**) were obtained, with isolated yields ranging between 50 and 70 % (Table 1).[20] These results allowed to us to prepare bispyrazoles (**17a**) and (**17b**) by reaction of compound (**1a**) with ethylene glycol and thioethylene glycol, respectively.[21] These compounds are useful precursors of chelating agents for Gd(III) and other lanthanides with potential interest as NMR contrast agents (Figure 2).[8,22]



17a: X = O
17b: X = S

Figure 2

In summary, we presented a study on the reactivity of 4-chloromethylpyrazoles with weak nucleophiles such as amides, carbamates, ureas, azoles, alcohols and thiols. In all cases, the corresponding *N*-monoalkylation products of amides, *tert*-butyl carbamate, ureas and azoles were isolated. When amides, ureas and carbamates were used as nucleophiles, the corresponding *O*-alkylation products were not observed. Remarkably, the presence of catalysts or basic medium was not required. The procedures described herein may provide a convenient method for the introduction of a 4-pyrazolylmethyl group into molecules containing a variety of functional groups with weak nucleophilic character.

An illustration of the performance of these methods is shown with the synthesis of a novel series of metal ligands, which contain ethylene glycol and thioethylene glycol units between the pyrazole rings.

ACKNOWLEDGEMENTS

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6. A stream of dry hydrogen chloride was passed through a solution of **2a** or **2b** (4.35 mmol or 16 mmol) and paraformaldehyde (4.35 mmol or 16 mmol) in 1,2-dichloroethane (4 mL or 8 mL) until saturation of the solution, and the reaction mixture was refluxed for 2 h. Subsequently, the reaction was cooled to room temperature and water (5 mL or 10 mL) was added. The water layer was made alkaline with Na_2CO_3 and extracted with CH_2Cl_2 (stabilized with amilene). The combined organic extracts were dried with $MgSO_4$ and evaporated *in vacuo*.
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9. **(Methoxycarbonylmethyl-{2-[5-methyl-3-phenyl-4-(propionylaminomethyl)pyrazol-1-yl]ethyl} amino)acetic acid methyl ester (3):** (mp 80-82 °C, CH_2Cl_2 / Hexane). Anal. Calcd for $C_{22}H_{30}N_4O_5$: C, 61.38; H, 7.02; N, 13.01. Found: C, 60.98; H, 6.96; N, 12.90. HRMS (EI) calcd for $C_{22}H_{30}N_4O_5$ [M^+], 430.2209 found 430.2195. IR (ATR): ν 3246, 1745, 1730, 1193 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55 (2 H, dd, *J* = 8.5, 1.4 Hz), 7.40-7.32 (3 H, m), 5.5 (1 H, br s), 4.37 (2 H, d, *J*= 4.5 Hz), 4.20 (2 H, t, *J* = 6.4 Hz), 3.67 (6 H, s), 3.49 (4 H, s), 3.20 (2 H, t, *J* = 6.4 Hz), 2.33 (3 H, s), 2.14 (2 H, q, *J* = 7.6 Hz), 1.10 (3 H, t, *J* = 7.6 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.3, 171.5, 149.6, 139.4, 133.4, 128.5, 127.6, 127.5, 111.8, 55.5, 54.6, 51.5, 48.4, 33.9, 29.4, 9.7, 9.5 ppm. **({2-[4-(Benzoylaminomethyl)-5-methyl-3-phenylpyrazol-1-yl]ethyl}methoxycarbonylmethyl-amino)acetic acid methyl ester (4):** (mp 43-44 °C, toluene). Anal. Calcd for $C_{26}H_{30}N_4O_5$: C, 65.26; H, 6.32; N, 11.71. Found: C, 65.20; H, 6.33; N, 11.67. IR (ATR): ν 3291, 1731, 1644 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 (2 H, dd, *J* = 8.8, 1.5 Hz), 7.60 (2 H, dd, *J* = 8.3, 1.2 Hz), 7.47-7.30 (6 H, m), 6.24 (1 H, br s), 4.58 (2 H, d, *J* = 4.5 Hz), 4.22 (2 H, t, *J* = 6.4 Hz), 3.63 (6 H, s), 3.49 (4 H, s), 3.21 (2 H, t, *J* = 6.4 Hz), 2.37 (3 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 167.1, 149.8, 139.6, 131.9, 131.3, 128.6, 128.5, 128.3, 127.7, 127.5, 126.8, 55.6, 54.6, 51.5, 48.4, 34.6, 9.6 ppm. MS *m/z* (%):

478 (M^+, 1), 357 (3), 187 (24), 174 (40), 128 (54), 105 (100), 77 (67).

10 **({2-[4-(*tert*-Butoxycarbonylaminomethyl)-5-methyl-3-phenylpyrazol-1-yl]ethyl}methoxycarbonylmethylamino)acetic acid methyl ester (5):** (as an oil) HRMS (EI) calcd for $C_{24}H_{34}N_4O_6$ [M^+] 474.2470, found 474.2486. IR (ATR): *v* 3385, 1738, 1703 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57 (2 H, dd, *J* = 8.5, 1.4 Hz), 7.41-7.30 (3 H, m), 4.53 (1 H, br s), 4.24 (2 H, d, *J* = 4.2 Hz), 4.20 (2 H, t, *J* = 6.5 Hz), 3.68 (6 H, s), 3.48 (4 H, s), 3.19 (2 H, t, *J* = 6.5 Hz), 2.34 (3 H, s), 1.45 (9 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 155.3, 149.7, 139.3, 133.4, 128.4, 127.5, 127.5, 112.2, 79.5, 55.4, 54.5, 51.4, 48.4, 34.6, 28.2, 9.4 ppm.

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15. ***N*-(3-Methyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)propionamide (6):** (mp 125-126 °C, toluene). Anal. Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found: C,68.80; H, 6.904; N, 17.07. IR (ATR): *v* 3304, 1637 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.81 (1 H, s), 7.61 (2 H, dd, *J* = 7.5, 1.5 Hz), 7.41 (2 H, m), 7.25 (1 H, m), 5.57 (1 H, br s), 4.33 (2 H, d, *J* = 5.3 Hz), 2.32 (3 H, s), 2.22 (2 H, q, *J* = 7.5 Hz), 1.17 (3 H, t, *J* = 7.5 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.4, 148.9, 139.7, 129.2, 126.6, 125.9, 118.5, 118.1, 33.3, 29.5, 11.7, 9.7 ppm. MS *m/z* (%): 243 (M^+, 48), 186 (39), 170 (100), 158 (25), 77 (67). ***N*-(3-Methyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)benzamide (7):** (mp 128-129 °C, CH_2Cl_2 / Hexane). Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42. Found: C, 73.72; H, 5.85; N, 14.28. IR (ATR): *v* 3289, 1625 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.85 (1 H, s), 7.77 (2 H, dd, *J* = 7.8, 1.4 Hz), 7.60 (2 H, dd, *J* = 7.6, 1.4 Hz), 7.46-7.37 (5 H, m), 7.26-7.23 (1 H, m), 6.33 (1 H, br s), 4.52 (2 H, d, *J* = 5.3 Hz), 2.35 (3 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.1, 149.0, 139.8, 134.2, 131.5, 129.3, 128.5, 126.8, 126.7, 126.0, 118.6, 117.9, 34.0, 11.8 ppm. MS *m/z* (%): 291 (M+, 30), 186 (11), 170 (70), 105 (70), 77 (100).

16. **1-(3-Methyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)-3-phenylurea (8):** (mp 177-178 °C, CH_2Cl_2 / Hexane). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.30; H, 5.92; N, 18.18. IR (ATR): *v* 3290, 1623, 1598 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.38 (1 H, s), 8.29 (1 H, s), 7.74 (2 H, dd, *J* = 7.8, 0.8 Hz), 7.44 (2 H, apparent t, *J* = 8.4, 7.6 Hz), 7.38 (2 H, dd, *J* = 7.7, 0.7 Hz), 7.22 (3 H, m), 6.87 (1 H, t, *J* = 7.3 Hz), 6.35 (1 H, t, *J* = 5.2 Hz), 4.17 (2 H, d, *J* = 5.4 Hz), 2.25 (3 H, s) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ 155.0, 148.3, 140.4, 139.6, 129.4, 128.6, 126.9, 125.4, 121.0,

119.8, 117.6, 117.6, 33.0, 11.7 ppm. MS *m/z* (%): 306 (M^+, 11), 171 (64), 93 (100), 77 (54). **1-Ethyl-3-(3-methyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)urea (9a):** (mp 151-152 °C, CH_2Cl_2 / Hexane). Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.32; H, 6.964; N, 21.38. IR (ATR): *v* 3308, 1615, 1561 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 (1 H, s), 7.61 (2 H, dd, *J* = 7.7, 1.2 Hz), 7.41 (2 H, m), 7.23 (1 H, m), 4.37 (1 H, br s), 4.27 (2 H, s), 3.22 (2 H, q, *J* = 7.1 Hz), 2.33 (3 H, s), 1.14 (3 H, t, *J* = 7.1 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.2, 148.8, 139.7, 129.2, 126.3, 125.8, 119.1, 118.3, 35.0, 34.2, 15.3, 11.6 ppm. MS *m/z* (%): 258 (M^+, 55), 186 (58), 171 (74), 158 (68), 77 (100), 51 (36). **1-Ethyl-1-(3-methyl-1-phenyl-1*H*-pyrazol-4-ylmethyl)urea (9b):** (mp 124-125 °C, CH_2Cl_2 / Hexane). Anal. Calcd for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.69. Found: C, 64.58; H, 6.86; N, 21.56. IR (ATR): *v* 3424, 3211, 1632, 1598 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 (1 H, s), 7.63 (2 H, dd, *J* = 8.6, 1.2 Hz), 7.42 (2 H, m), 7.24 (1 H, m) 4.45 (2 H, s), 4.37 (2 H, s), 3.29 (2 H, q, *J* = 7.2 Hz), 2.33 (3 H, s), 1.18 (3 H, t, *J* = 7.2 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.3, 148.6, 139.8, 129.2, 126.4, 125.6, 118.4, 118.0, 41.6, 40.3, 13.1, 11.9 ppm. MS *m/z* (%): 258 (M^+, 26), 186 (32), 171 (100), 77 (69).

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18. **4-Imidazol-1-ylmethyl-3-methyl-1-phenyl-1*H*-pyrazole (10):** (as an oil) HRMS (EI) calcd for $C_{14}H_{14}N_4$ [M^+] 238.1216, found 238.1217. IR (ATR): *v* 1599, 1505 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.75 (1 H, s), 7.61 (2 H, m), 7.54 (1 H, s), 7.41 (2 H, m), 7.27 (1 H, m), 7.08 (1 H, s), 6.93 (1 H, s), 5.03 (2 H, s), 2.26 (3 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.5, 139.4, 136.6, 129.4, 129.1, 126.5, 126.1, 118.6, 118.4, 116.1, 40.7, 11.4 ppm.
19. **3-Methyl-1-phenyl-4-pyrazol-1-ylmethyl-1*H*-pyrazole (11):** (as an oil) HRMS (EI) calcd for $C_{14}H_{14}N_4$ [M^+] 238.1216, found 238.1209. IR (ATR): *v* 1599, 1569 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.83 (1 H, s), 7.61 (2 H, dd, *J* = 7.6, 1.2 Hz), 7.53 (1 H, d, *J* = 1.7 Hz), 7.41 (2 H, m), 7.37 (1 H, d, *J* = 2.3 Hz), 7.24 (1 H, m), 6.26 (1 H, t, *J* = 2.1 Hz), 5.23 (2 H, s), 2.28 (3 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.9, 139.6, 139.3, 129.2, 128.3, 126.9, 126.0, 118.5, 116.4, 105.6, 45.8, 11.6 ppm. **3-Methyl-4-(4-nitro-imidazol-1-ylmethyl)-1-phenyl-1*H*-pyrazole (12):** (mp 140-142 °C, CH_2Cl_2 / Hexane). Anal. Calcd for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.63; N, 24.72. Found: C, 59.30; H, 4.637; N, 24.56. IR (ATR): *v* 3122, 1504, 1480 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.91 (1 H, s), 7.75 (1 H, d, *J* = 1.5 Hz), 7.63 (2 H, dd, *J* = 7.6, 1.2 Hz), 7.49 (1 H, d, *J* = 1.3 Hz), 7.46 (2 H, m), 7.31 (1 H, m), 5.12 (2 H, s), 2.29 (3 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 148.8, 139.3, 135.4, 129.4, 127.3, 126.8, 118.9, 118.7, 113.7, 42.2, 11.7 ppm. MS *m/z* (%): 283 (M^+, 11), 171 (100), 77 (42).
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21. **{[2-(4-Ethoxymethyl-5-methyl-3-phenylpyrazol-1-yl)ethyl]methoxycarbonylmethylamino}-acetic acid methyl ester (13):** (as an oil) HRMS (EI) calcd for $C_{21}H_{29}N_3O_5$ [M^+] 403.2100, found 403.2101. IR (ATR): ν 1746, 1437, 1202, 1004, 796, 777 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.71, (2 H, d, J = 8.4 Hz), 7.42-7.32 (3 H, m), 4.34 (2 H, s), 4.21 (2 H, apparent t, J = 7.0, 6.6 Hz), 3.67 (6 H, s), 3.55 (2 H, q, J = 7.0 Hz), 3.54 (4 H, s), 3.20 (2 H, apparent t, J = 7.0, 6.6 Hz), 2.36 (3 H, s), 1.26 (3 H, t, J = 7.0 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4, 150.7, 139.5, 133.6, 128.2, 127.8, 127.3, 112.7, 64.9, 62.5, 55.4, 54.3, 51.4, 48.2, 15.1, 9.4 ppm.

{[2-(4-Benzyloxymethyl-5-methyl-3-phenylpyrazol-1-yl)ethyl]methoxycarbonylmethylamino}-acetic acid methyl ester (14): (as an oil) HRMS (EI) calcd for $C_{26}H_{31}N_3O_5$ [M^+] 465.2264, found 465.2265. IR (ATR): ν 1746, 1454, 1359, 1202, 1064, 703 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 (2 H, d, J = 8.1 Hz), 7.42-7.28 (8 H, m), 4.56 (2 H, s), 4.39 (2 H, s), 4.22 (2 H, apparent t, J = 7.1, 6.3 Hz), 3.67 (6 H, s), 3.51 (4 H, s), 3.19 (2 H, apparent t, J = 7.0, 6.4 Hz), 2.32 (3 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.4, 150.8, 139.8, 138.2, 133.5, 128.2, 127.9, 127.8, 127.5, 127.3, 112.5, 71.7, 62.0, 55.5, 54.4, 51.4, 48.3, 9.5 ppm.

{Methoxycarbonylmethyl-[2-(5-methyl-3-phenyl-4-propylsulfanylmethylpyrazol-1-yl)ethyl]-amino}acetic acid methyl ester (15): (as an oil) HRMS (EI) calcd for $C_{22}H_{31}N_3O_4S$ [M^+] 403.2028, found 403.2027. IR (ATR): ν 1748, 1436, 1203, 784, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.71 (2 H, dd, J = 8.4, 1.4 Hz), 7.43-7.26 (3 H, m), 4.20 (2 H, apparent t, J = 6.8, 6.6 Hz), 3.67 (6 H, s), 3.66 (2 H, s), 3.49 (4 H, s), 3.19 (2 H, t, J = 6.6 Hz), 2.45 (2 H, dd, J = 7.4, 7.2 Hz), 2.35 (3 H, s), 1.57 (2 H, m), 0.93 (3 H, t, J = 7.3 Hz) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 149.8, 138.6, 133.7, 128.3, 127.9, 127.3, 122.9, 55.47, 54.4, 51.4, 48.5, 34.3, 25.6, 22.6, 13.3, 9.6 ppm.

{[2-(4-Benzylsulfanylmethyl-5-methyl-3-phenylpyrazol-1-yl)ethyl]methoxycarbonylmethyl-amino}acetic acid methyl ester (16): (as an oil) HRMS (EI) calcd for $C_{26}H_{31}N_3O_4S$ [M^+] 481.2028, found 481.2025. IR (ATR): ν 1748, 1452, 1436, 1202, 785, 701 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.61 (4 H, dd, J = 8.2, 1.7 Hz), 7.34-7.26 (6 H, m), 4.18 (2 H, apparent t, J = 6.8, 6.5 Hz), 3.69 (2 H, s), 3.67 (6 H, s), 3.57 (2 H, s), 3.47 (4 H, s), 3.16 (2 H, apparent t, J = 6.8, 6.7 Hz), 1.63 (3 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 149.7, 138.9, 138.3, 133.6, 128.7, 128.3, 127.8, 127.3, 126.8, 111.2, 55.5, 54.4, 51.5, 48.5, 36.9, 25.5, 9.5 ppm.

22. **({2-[4-(2-{1-[2-(Bismethoxycarbonylmethylamino)ethyl]-5-methyl-3-phenyl-1*H*-pyrazol-4-yl-methoxy}ethoxymethyl)-5-methyl-3-phenylpyrazol-1-yl]ethyl}methoxycarbonylmethylamino) acetic acid methyl ester (17a):** (as an oil) HRMS (EI) calcd for $C_{40}H_{53}N_6O_{10}$ [M^+] 777.3823, found 777.3826. IR (ATR): ν 1736, 1434, 1198, 1118, 1080, 1033, 775, 701 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.72 (4 H, d, J = 8.5 Hz), 7.36-7.29 (6 H, m), 4.41 (4 H, s), 4.20 (4 H, apparent t, J = 7.1, 6.5

Hz), 3.67 (16 H, s), 3.51 (8 H, s), 3.19 (4 H, apparent t, *J* =6.9, 6.7 Hz), 2.32 (6 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 150.9, 139.7, 133.6, 128.3, 127.9, 127.4, 112.5, 68.8, 63.1, 55.5, 54.4, 51.5, 48.3, 9.5 ppm.

({2-[4-(2-{1-[2-(Bismethoxycarbonylmethylamino)ethyl]-5-methyl-3-phenyl-1*H*-pyrazol-4-yl-methylsulfanyl}ethylsulfanylmethyl)-5-methyl-3-phenylpyrazol-1-yl]ethyl}methoxycarbonyl-methylamino)acetic acid methyl ester (17b): (as an oil) HRMS (EI) calcd for $C_{40}H_{53}N_6O_8S_2$ [M^+] 809.3366, found 809.3342. IR (ATR): *ν* 1746, 1436, 1202, 786, 702 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.66 (4 H, dd, *J* = 8.4, 1.1 Hz), 7.41-7.25 (6 H, m), 4.20 (4 H, apparent t, *J* = 6.9, 6.4 Hz), 3.67 (12 H, s), 3.64 (4 H, s), 3.48 (8 H, s), 3.19 (4 H, apparent t, *J* = 6.8, 6.5 Hz), 2.62 (4 H, s), 2.33 (6 H, s) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.5, 149.8, 138.8, 133.6, 128.4, 128.0, 127.5, 111.4, 55.5, 54.4, 51.5, 48.5, 32.1, 25.8, 9.6 ppm.

23 a) 'The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging', ed. by A. E Merbach and E. Tóth, John Wiley & Sons, Ltd., England, 2001. b) 'Contrast Agents I. Magnetic Resonance Imaging', ed. by W. Krause, *Top. Curr. Chem.*, 2002, **221**, 1.