6.74 (s, 1 H), 5.03 (d, 2 H, J = 2.4), 4.15-4.11 (m, 1 H), 3.95 (dd, 1 H, J = 11.7, 9.0), 3.84 (dd, 1 H, J = 11.8, 4.8), 3.53 (dq, 1 H, J = 14.3, 7.3), 3.11 (dq, 1 H, J = 14.2, 7.1), 3.03 (dd, 1 H, J = 14.4, 3.7), 2.66 (dd, 1 H, J = 14.3, 8.6), 1.12 (t, 3 H, J = 7.2); ^{13}C NMR δ 165.30 (C=O), 152.40 (C=O), 50.52 (1), 50.39 (2), 44.78 (2), 35.84 (2), 31.36 (2), 12.26 (3). Anal. Calcd for $C_{23}H_{22}Cl_2N_4O_2$: C, 60.4; H, 4.8; N, 12.2. Found: C, 60.1; H, 4.6; N, 12.0.

12d: yield, 18%; ^{1}H NMR δ 7.76-7.12 (m, 8 H), 7.48 (s, 1 H), 6.72 (s, 1 H), 5.06 (s, 2 H), 4.53 (t, 1 H, J = 8.8), 4.37 (dd, 1 H, J = 9.0, 5.8), 4.32-4.27 (m, 1 H), 3.79 (dq, 1 H, J = 14.2, 7.2), 3.27 (dq, 1 H, J = 14.1, 7.1), 3.05 (dd, 1 H, J = 14.5, 3.9), 2.72 (dd, 1 H, J = 14.4, 8.7), 1.23 (t, 3 H, J = 7.1); ^{13}C NMR δ 173.00, 159.25, 71.09 (2), 55.05 (1), 50.88 (2), 37.84 (2), 30.76 (2), 12.51 (3). Anal. Calcd for $C_{23}H_{22}Cl_2N_4O_2$: C, 60.4; H, 4.8; N, 12.2. Found: C, 60.2; H, 4.8; N, 12.2.

(*S*)-1-(2,4-Dichlorobenzoyl)-3-isobutyl-4-[(1′-benzyl-4′-imidazolyl)methyl]-2-imidazolidinone (13e) and 12e. 13e: yield, 74%; ^{1}H NMR δ 7.49 (s, 1 H), 7.46-7.13 (m, 8 H), 6.75 (s, 1 H), 5.04 (d, 2 H, J = 2.8), 4.14-4.07 (m, 1 H), 3.96 (dd, 1 H, J = 11.7, 8.8), 3.85 (dd, 1 H, J = 11.7, 4.5), 3.27 (dd, 1 H, J = 14.0, 9.4), 3.03 (dd, 1 H, J = 14.3, 3.8), 2.89 (dd, 1 H, J = 14.0, 5.9), 2.65 (dd, 1 H, J = 14.3, 8.7), 2.00-1.92 (m, 1 H), 0.89 (d, 3 H, J = 6.7), 0.84 (d, 3 H, J = 6.6); ^{13}C NMR δ 165.52 (C=O), 152.90 (C=O), 51.24 (1), 50.49 (2), 48.29 (2), 44.82 (2), 31.18 (2), 25.95 (1), 19.89 (3), 19.32 (3). Anal. Calcd for $C_{25}H_{26}Cl_2N_4O_2$: C, 61.9; H, 5.4; N, 11.5. Found: C, 61.8; H, 5.4; N, 11.1.

12e: yield, 15%; ^{1}H NMR δ 7.73-7.13 (m, 8 H), 7.47 (s, 1 H), 6.72 (s, 1 H), 5.05 (s, 2 H), 4.53 (t, 1 H, J = 8.8), 4.39 (dd, 1 H, J = 9.0, 5.1), 4.29-4.25 (m, 1 H), 3.58 (dd, 1 H, J = 13.8, 9.3), 3.05-2.98 (m, 2 H), 2.71 (dd, 1 H, J = 14.4, 8.8), 2.11-2.05 (m, 1 H), 0.95 (d, 3 H, J = 6.7), 0.92 (d, 3 H, J = 6.6); ^{13}C NMR δ 173.50, 160.25, 70.82 (2), 55.56 (1), 50.76 (2), 49.94 (2), 30.26 (2), 26.30 (1), 20.11 (3), 19.66 (3). Anal. Calcd for $C_{25}H_{26}Cl_2N_4O_2$: C, 61.9; H, 5.4; N, 11.5. Found: C, 61.9; H, 5.3; N, 11.4.

Conversion of 13d and 13e to the Corresponding *N*-Methylimidazolium Iodides 14d and 14e. A solution of **13d** (0.24 g, 0.5 mmol) and methyl iodide (0.16 mL, 2.5 mmol) in acetone was stirred at 60 °C for 5 h. The reaction mixture was then evaporated, and the residue was crystallized from toluene/methanol to give **14d**, 0.28 g, 89% yield: ^{1}H NMR δ 9.65 (s, 1 H), 7.61 (s, 1 H), 7.50-7.26 (m, 8 H), 5.51 (d, 1 H, J = 14.5), 5.44 (d, 1 H, J = 14.4), 4.29-4.24 (m, 2 H), 3.98 (s, 3 H), 3.76 (d, 1 H, J = 8.0), 3.51 (dq, 1 H, J = 14.5, 7.2), 3.27 (d, 1 H, J = 13.9), 3.08 (dq, 1 H, J = 14.3, 7.0), 2.96 (dd, 1 H, J = 11.1, 8.4), 1.10 (t, 3 H, J = 7.1); ^{13}C NMR δ 165.53 (C=O), 152.30 (C=O), 53.17 (2), 48.98 (1), 45.27 (2), 36.67 (2), 35.20 (3), 27.62 (2), 12.81 (3).

As described for the preparation of **14d**, **13e** (0.37 g, 0.8 mmol) was transformed into crude methiodide **14e** (0.49 g, 105%): ^{1}H NMR δ 9.65 (s, 1 H), 7.53 (s, 1 H), 7.47-7.07 (m, 8 H), 5.45 (d, 1 H, J = 14.4), 5.38 (d, 1 H, J = 14.4), 4.22-4.12 (m, 2 H), 3.90 (s, 3 H), 3.73 (d, 1 H, J = 8.2), 3.20 (d, 1 H, J = 15.0), 3.16 (dd, 1 H, J = 14.1, 9.4), 2.78 (dd, 1 H, J = 14.1, 5.9), 2.73 (dd, 1 H, J = 15.2, 8.1), 1.85-1.78 (m, 1 H), 0.80 (d, 3 H, J = 6.6), 0.74 (d, 3 H, J = 6.5); ^{13}C NMR δ 165.64 (C=O), 152.69 (C=O), 53.17 (2), 49.62 (1), 48.76 (2), 45.23 (2), 35.15 (3), 27.28 (2), 26.46 (1), 20.09 (3), 19.56 (3).

(*S*)-3-Ethyl-4-(1′-methyl-5′-imidazolyl)-2-imidazolidinone (15a). A suspension of imidazolium salt **14d** (0.24 g, 0.4 mmol), ammonium formate (15 g), and 10% Pd/C (0.12 g) in methanol (40 mL) was refluxed for 6 h. After being cooled to room temperature, the reaction mixture was filtered and evaporated, the residue was dissolved in a saturated sodium bicarbonate solution (20 mL), and the pH was adjusted to 8.5 with potassium carbonate. The aqueous phase was extracted with chloroform/2-propanol (2/1, 2 × 150 mL), and the combined phases were washed with sodium thiosulfate and evaporated. The residue was dissolved in 0.4 N NaOH (4 mL) and methanol (8 mL) and warmed at 70 °C for 0.5 h, the solution was then extracted with chloroform/2-propanol (2/1, 2 × 50 mL), and the combined organic phase was dried, filtered, and evaporated. Crystallization of the residue from toluene gave cyclic urea **15a**, 0.06 g, 72% yield: mp 143-144 °C; ^{1}H NMR δ 7.43 (s, 1 H), 6.82 (s, 1 H), 4.91 (s, 1 H), 3.99-3.95 (m, 1 H), 3.66-3.55 (m, 1 H), 3.59 (s, 3 H), 3.52-3.48 (m, 1 H), 3.12 (ddd, 1 H, J = 8.7, 5.8, 1.1), 3.02 (dq, 1 H, J = 14.3, 7.1), 2.98 (dd, 1 H, J = 11.8, 3.8), 2.70 (dd, 1 H, J = 15.2, 9.7), 1.14 (t, 3 H, J = 7.2); ^{13}C NMR δ 161.79 (C=O), 138.20, 127.33, 127.16, 53.80 (1), 43.96 (2), 35.76 (2), 31.37 (3), 27.12 (2), 12.90 (3); $[\alpha]^{20}_D$ +84.1° (c 0.42, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}N_4O$: C, 57.7; H, 7.7; N, 26.9. Found: C, 57.7; H, 7.5; N, 26.4.

(*S*)-3-Isobutyl-4-(1′-methyl-5′-imidazolyl)-2-imidazolidinone (15b). As described for the preparation of **15a**, imidazolium salt **14e** (0.27 g, 0.4 mmol) was transformed into **15b**, 0.08 g, 75% yield: mp 157-158 °C; ^{1}H NMR δ 7.43 (s, 1 H), 6.81 (s, 1 H), 5.11 (s, 1 H), 3.95-3.89 (m, 1 H), 3.58 (s, 3 H), 3.51 (t, 1 H, J = 8.8), 3.29 (dd, 1 H, J = 14.1, 9.5), 3.14 (dd, 1 H, J = 8.6, 5.6), 2.97 (dd, 1 H, J = 15.2, 3.7), 2.80 (dd, 1 H, J = 14.1, 5.8), 2.68 (dd, 1 H, J = 15.2, 9.9), 1.92-1.86 (m, 1 H), 0.95 (d, 3 H, J = 6.7), 0.91 (d, 3 H, J = 6.7); ^{13}C NMR δ 162.12 (C=O), 138.15, 127.26, 127.05, 54.50 (1), 48.34 (2), 43.83 (2), 31.34 (3), 26.92 (1), 26.55 (2), 20.27 (3), 19.72 (3); $[\alpha]^{20}_D$ +79.1° (c 1.06, $CHCl_3$). Anal. Calcd for $C_{12}H_{20}N_4O$: C, 61.0; H, 8.5; N, 23.7. Found: C, 60.6; H, 8.4; N, 23.2.

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N-Substitution of 2-Methyl-4(5)-nitro-1*H*-imidazole: A New, High-Yielding Method for Preparation of 4-Nitro Isomers

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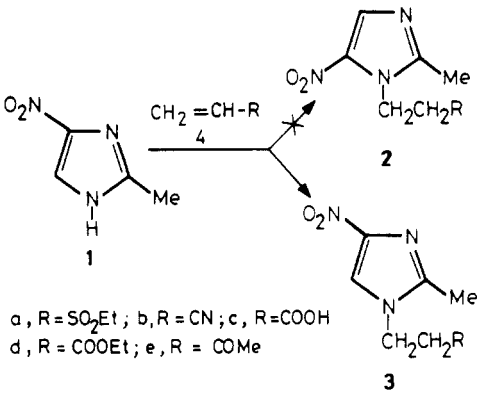
N-Substituted products from 2-methyl-4(5)-nitro-1*H*-imidazole (1) are of great utility as chemotherapeutic



agents. Tinidazole and metronidazole, belonging to the 5-nitro series, have been widely used in the treatment of protozoal infections like trichomoniasis.[1,2] The 4-nitro compounds are gaining pharmacological significance as immunosuppressants,[3] aldehyde dehydrogenase inhibitors,[4] potential radio sensitizers,[5] and radiotherapy synergists.[6]

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Table I. Addition of 1 to 4b under Varying Conditions

solvent	acid or base	temp, °C	time, h	isolated yield, %
methanol	NaOMe	reflux	15	55
ethanol	glacial AcOH	reflux	40	9
2-propanol	$NaOPr^i$	reflux	15	62
ethanol	glacial $AcOH/Cu(OAc)_2$	reflux	40	10
water	K_2CO_3	reflux	15	45
DMF		135–140	10	70
DMF	Py	135–140	10	80
DMSO	Py	135–140	10	90

Normally these nitroimidazoles are synthesized by the reactions of 1 with suitable alkyl halides, sulfates, or tosylates. Depending on the reaction conditions, especially pH, either N-alkylated 5-nitro-1*H*-imidazoles (**2**) or the corresponding 4-nitro isomers (**3**) or mixtures of both are formed.[7]

Recently we have observed the exclusive formation of 1-[2-(ethylsulfonyl)ethyl]-2-methyl-4-nitro-1*H*-imidazole (**3a**) on the reaction of 1 with ethyl vinyl sulfone.[8] We now report that this method of addition of 1 to suitable Michael acceptors (**4**) can be employed as a general method for the preparation of a variety of 4-nitro isomers of N-substituted imidazoles. Several Michael acceptors like acrylonitrile, acrylic acid, ethyl acrylate, and methyl vinyl ketone have been reacted with 1, giving exclusively the 4-nitro isomer of the corresponding N-substituted products (**3b–e**) in almost quantitative yields.

The reactions have been carried out under a variety of conditions by changing solvents, varying base strengths, and using Lewis acid catalysts. The best yields were obtained in DMSO–pyridine medium at 135–140 °C, the yield of the crude product being almost quantitative. The effect of reaction conditions on the yield has been shown in Table I by a representative reaction of 1 with **4b**. The 5-nitro isomer was never detected in any of the above reactions, irrespective of the conditions.

The structures of the N-substituted 4-nitroimidazoles (**3**) have been unequivocally established on the basis of spectral data (^{13}C and ^1H NMR and mass spectra). In the literature, the structures of various *N*-alkyl-4- and -5-nitroimidazoles have been unequivocally established by using ^1H and ^{13}C NMR and mass spectral data. The ^{13}C NMR chemical shift values of the ring carbon atoms have been used to assign the position of the nitro group.[9] For example, the chemical shifts of carbon C-5 are about 122 ppm for the 4-nitro isomers and 139 ppm for the 5-nitro isomers, whereas chemical shifts for carbon C-4 are 145 ppm for the 4-nitro and 133 ppm for the corresponding 5-nitro compounds. As can be seen from Table II, the ^{13}C chemical shift values for **3a–e** are in exactly the same range, 122.0–122.7 ppm for the C-5 carbon and 145.95–146.5 for the C-4 carbon atom, thus establishing the position of the nitro group. On comparison, the corresponding values for compounds **2a** (5-nitro isomer of **3a**) and **2b** (5-nitro isomer of **3b**) are 138.7, 133.2 and 139.2, 134.1 ppm.

Solvent-induced chemical shifts $\Delta\delta$ (DMSO-d_6–$CDCl_3$) in ^1H NMR provide another tool that has been used to establish the position of the NO_2 group in the alkylimidazole group of compounds.[10] It has been established that observation of $\Delta\delta$ values of above 0.45 ppm for the nitroimidazole ring proton would indicate the position of the nitro group to be 4 and compounds showing $\Delta\delta$ values of less than 0.3 ppm would be 5-nitroimidazoles. In keeping with these observations, compounds **3a–e** exhibit $\Delta\delta$ (DMSO-d_6–$CDCl_3$) values of 0.4–0.6, indicating clearly that these compounds are 4-nitro isomers. The corresponding values for compounds **2a** and **2b** are 0.06 and 0.04.

In the mass spectra, the intensity of the M^+-NO_2 fragment has been used decisively to establish the position of the nitro group,[10] the 5-nitroimidazoles exhibiting a more intense M^+-NO_2 fragment peak than their 4-nitro isomers. Mass spectral data of compounds **3a–e** indicated negligible intensities for M^+-NO_2 peaks, confirming the 4-nitro structure. On the contrary, these peaks are intense in compounds **2a** and **2b**. Thus, all the above spectral data, as illustrated in Table II, unequivocally establish the structures of the Michael adducts of 1 to be *N*-alkyl-4-nitroimidazoles.

There are several useful and interesting features of this reaction. Unlike the other known methods in literature, this method invariably and exclusively produces the 4-nitro isomer irrespective of the pH of the reaction medium. Further, since the *N*-alkyl substituents have active functional groups, this could provide access to a large number of potentially useful new compounds. The known literature methods[7] are either unsuitable for preparations of such compounds with functionalized alkyl substituents with three or more carbon atoms, or cumbersome and expensive.

Table II. Analytical Data for Compounds 2a,b and 3a–e

compd no.	yield, %	mp, °C	^1H NMR: δ (DMSO-d_6)	^{13}C NMR: δ (DMSO-d_6)	MS:[a] *m/z*
2a		126–127	8.04 (1 H, s), 4.72 (2 H, t), 3.68 (2 H, t), 3.20 (2 H, q), 2.52 (3 H, s), 1.24 (3 H, t); H-4 $\Delta\delta$ (DMSO-d_6–$CDCl_3$) 0.06	6.2, 14.1, 39.3, 47.2, 50.0, 133.2, 138.7, 152	247 (M^+, 100), 201 ($M^+ - NO_2$, 800)
3a	85	135–138	8.40 (1 H, s), 4.45 (2 H, t), 3.72 (2 H, t), 3.15 (2 H, q), 2.40 (3 H, s), 1.25 (3 H, t); H-5 $\Delta\delta$ (DMSO-d_6–$CDCl_3$) 0.60	6.1, 12.71, 39.82, 47.66, 50.41, 122.7, 146.3	247 (M^+, 100), 201 ($M^+ - NO_2$, 3)
2b		82–83	8.05 (1 H, s), 4.61 (2 H, t), 3.22 (2 H, t), 2.50 (3 H, s); H-4$\Delta\delta$ (DMSO-d_6–$CDCl_3$) 0.04	13.70, 18.08, 41.43, 119.17, 134.1, 139.20, 152.48	180 (M^+, 100), 134 ($M^+ - NO_2$, 110)
3b	90	114–116	8.40 (1 H, s), 4.41 (2 H, t), 3.20 (2 H, t), 2.48 (3 H, s); H-5 $\Delta\delta$ (DMSO-d_6–$CDCl_3$) 0.58	11.84, 18.36, 41.98, 118.7, 122.0, 146.1, 146.5	180 (M^+, 100), 134 ($M^+ - NO_2$, negligible)
3c	91	216–218	8.35 (1 H s), 4.20 (2 H, t), 2.85 (2 H, t), 2.40 (3 H, s)	12.31, 35.41, 41.62, 122.43, 145.76, 146.0, 173.0	199 (M^+, 100), 153 ($M^+ - NO_2$, 4)
3d	96	syrupy liq[b]	8.30 (1 H, s), 4.05–4.20 (4 H, m), 2.92 (2 H, t), 2.40 (3 H, s), 1.20 (3 H, t); H-5 $\Delta\delta$ (DMSO-d_6–$CDCl_3$) 0.50	12.30, 13.71, 34.23, 42.16, 60.83, 122.41, 145.95, 146.41, 171.4	227 (M^+, 100), 181 ($M^+ - NO_2$, 3)
3e	92	92–94	8.24 (1 H, s), 4.21 (2 H, t), 3.12 (2 H, t), 2.40 (3 H, s), 2.16 (3 H, s); H-5 $\Delta\delta$ (DMSO-d_6–$CDCl_3$) 0.40	12.30, 29.56, 41.23, 42.63, 122.57, 146.23, 146.51, 207.36	197 (M^+, 100), 151 ($M^+ - NO_2$, negligible)

[a] Intensities are approximate and relative to the M^+ peak as 100%. [b] Homogeneous by TLC; found to be identical with the compound obtained by esterifying **3c** with ethanol.

Some publications have reported that the adducts obtained by addition of 1 to Michael acceptors are 5-nitro isomers.[11-14] The present paper unequivocally establishes that the product of Michael addition actually is the 4-nitro isomer and not the 5-nitro isomer. Another literature publication[15] reports the formation of the 4-nitro isomer in very low yield (9%) on treatment of 1 with **4a** under prolonged reflux in water at a pH of 4.25. By contrast, the method reported in this paper (DMSO–pyridine) gives an 85% yield.

In conclusion, this work describes the regiospecific synthesis of biologically important N-substituted 4-nitro-1*H*-imidazoles in near quantitative yields.

Experimental Section

General. Analytical. TLC was performed on silica gel plates with appropriate solvent systems. Melting points were recorded on a Mettler FP 800 Thermosystem and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a FT-NMR instrument (JEOL FX 60Q), and the mass spectra were obtained on a JEOL DX-300 double-focusing mass spectrometer.

General Procedure. A mixture of 1 (50 mmol), Michael acceptor reagent (**4**) (70 mmol), and pyridine (0.2 mL) was taken in dry DMSO (20 mL) and heated under nitrogen at 135–140 °C for 10 h. The solvent was removed under vacuum, the residue was taken up in EtOAc and washed with aqueous ammonia, followed by water, and the organic layer was evaporated, to get the crude products (**3**), which were crystallized from EtOAc. In the case of compound **3c**, the residue left after removal of DMSO was triturated with water and directly recrystallized from DMF–H_2O (1:1). The yields of crude products, which were practically pure and homogeneous on TLC, were almost quantitative. The yields of the crystallized products are given in the Table II.

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Registry No. 1, 696-23-1; **2a**, 19387-91-8; **2b**, 14885-27-9; **3a**, 25459-12-5; **3b**, 89128-08-5; **3c**, 16935-04-9; **3d**, 126664-27-5; **3e**, 126664-28-6; **4a**, 1889-59-4; **4b**, 107-13-1; **4c**, 79-09-4; **4d**, 140-88-5; **4e**, 78-94-4.

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Additions and Corrections

Vol. 54, 1989

Hubert Maehr,* Roxana Yang, Li-Na Hong, Chao-Min Liu, Marcos H. Hatada, and Louis J. Todaro. Microbial Products. 9. Roxaticin, a New Oxo Pentaene Antibiotic.

Page 3817. The legend for formulas 1–4 should read as follows:

1 Roxaticin

2a R=Me: Mycoticin A

2b R=Et: Mycoticin B

3 Roflamycoin

4a R=Me: Dermostatin A

4b R=Et: Dermostatin B

David StC. Black, Donald C. Craig, Olga Giitsidis, Roger W. Read,* Abdoreza Salek, and Mark A Sefton. Synthesis of Fused Polyazapolycyclic Compounds through Condensation of Diaminoalkanes with Carbonyl Compounds.

Page 4776. The ^{13}C NMR data for compounds 1 and 2 in Table V should be interchanged.

Page 4779, column 2, paragraph 1. The space group and other crystallographic data were incorrectly represented and should be replaced by the following:

Crystal data for 5: $C_8H_{14}N_8O_8$, M 349.39, triclinic, space group $P\bar{1}$, a 6.602 (6) Å, b 7.341 (2) Å, c 8.231 (3) Å, α 89.54 (2)°, β 74.56 (2)°, γ 66.15 (2)°, V 349.4 (2) Å^3, D_c 1.66 g cm^{-3}, Z 1, μ_{Mo} 1.39 cm^{-1}.

Paragraph 2. The graphite monochromatized molybdenum radiation used was λ 0.7107 Å. Reflexions with $I > 3\sigma(I)$ were considered observed. Reflexion weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o) = [\sigma^2(I_o) + (0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w = (\sum w\Delta^2/\sum wF_o^2)^{1/2}$.