obtained at −60 °C after reducing the filtrate to half-volume in vacuum. The total yield was 68%. It was recrystallized from hexane: mp 199–200 °C. Anal. Calc for $C_{25}H_{52}$: C, 85.23; H, 14.77. Found: C, 85.14; H, 14.86. IR (neat): 2950 vs, 1540 s, 1320 s. ^{1}H NMR ($CDCl_3$): δ 0.84 (s), 1.01 (s, br). ^{13}C NMR: δ 29.6, 30.1, 31.0, 35.6, 36.4. MS (CI with methane): m/z 351 (M − 1), 337 (M − 15), 267 (M − 85), 85 (base, M − 267).

Chlorination of 2. Compound **2** (50.0 mg, 0.14 mmol) was dissolved in 5 mL of CCl_4. The solution was cooled with an ice bath and irradiated with a 100-W incandescent bulb at a distance of about 10 cm. Chlorine was bubbled into the solution during this time. After 2 h, the solvent was completely removed in vacuum, giving 0.1686 g of a white solid, mp 70–80 °C. The gain in weight corresponded to an average formula of $C_{25}H_{28}Cl_{24}$ = 1152. Mass spectral analysis (CI) showed peaks up to m/z 867. The ^{1}H NMR spectrum showed residual H atoms as poorly resolved peaks at δ 6.4, 4.0, 2.7, and 1.6.

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Registry No. **1**, 126724-73-0; **2**, 126724-71-8; CO, 124-38-9; *t*-BuCH:CH_2, 558-37-2; *t*-BuLi, 594-19-4; C_2H_4, 74-85-1; $(EtO)_2CO$, 105-58-8; *t*-Bu$(CH_2)_2$Cl, 2855-08-5; (*t*-Bu$(CH_2)_2)_3$CCl, 126724-72-9; *i*-Bu_3Al, 100-99-2; (*t*-Bu$(CH_2)_2)_3$Al, 6918-10-1.

2-Imidazolidinones from 1,2-Amino Alcohols. Application to the Synthesis of a 2-Imidazolidinone Analogue of Pilocarpine

Taek Hyeon Kim and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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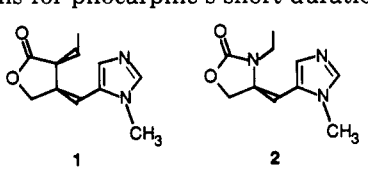
As a consequence of our finding that the imidazolyloxazolidinone **2**, the cyclic carbamate analogue of (+)pilocarpine (**1**), was equipotent to pilocarpine at muscarinic receptors,[1] we were led to prepare the corresponding imidazolidinone, the cyclic urea analogue. In our continuing search for efficacious and longer acting pilocarpine analogues, we projected that such a cyclic urea analogue would be significantly more stable to hydrolytic ring opening, one of the reasons for pilocarpine's short duration of action.



1 **2**

We planned to make use of our previous intermediate, N^a-ethyl-N^τ-benzylhistidinol (**4a**). This convenient chiral educt offers ease of preparation, on a large scale if necessary, and controlled regiochemistry in the imidazole ring. Conversion to the 1,2-diamine and cyclization to the 2-imidazolidinone was expected to proceed with facility through the conventional transformations of (1) protection of the secondary amine, (2) activation of the hydroxyl into a good leaving group, (3) displacement of this leaving group by azide ion, (4) reduction to the diamine, and (5) cyclization to the urea—five easy, straightforward steps. The reality, however, was quite different.

Our plan ran into problems from the outset, as shown in Scheme I. Attempts to selectively protect the secondary amine of histidinol **4** failed and gave a mixture of *N*-CBZ and *N,O*-bis-CBZ product **5**.[2] This mixture was difficult to separate; alternatively, selective hydrolysis of the *O*-CBZ group was attempted. No reaction occurred with $K_2CO_3/CH_3OH/H_2O$. Since selective cleavage of the benzyloxycarbonyl group from sulfur in a N,S-diprotected compound had been achieved by a brief treatment with sodium ethoxide,[3] we applied this process to our mixture. The product isolated in excellent yield was the known oxazolidinone **6**.

We next turned to a more stable N-protecting group which would avoid cyclic carbamate formation. The *N*-acetylhistidinol **7** was readily prepared by selective acetylation of the corresponding histidinol. However, all attempts to convert the hydroxyl into a leaving group, appropriate for displacement by azide ion, failed. Standard conditions were used for mesylate and tosylate formation;[4a] only completely water soluble products were formed. Similarly, various attempts to form the bromide[4b,d] or directly displace the hydroxyl with phthalimide/triphenylphosphine/diethyl azodicarboxylate[4c] also failed. In every reaction, the total product was completely water soluble. This behavior is probably due to the activated intermediate **8** undergoing instant intramolecular alkylation at the nucleophilic N^τ-imidazole nitrogen. The resulting quaternary salt **9** would of course be highly water soluble.

From these failures it became clear that we had to create a competing, and perhaps superior, nucleophilic site in the molecule. This was achieved along with a successful synthesis of the target imidazolidinones as shown in Scheme II. Our strategy was to attach an iminodicarbonyl group to the secondary amino function of histidinol **4**. This was to be accomplished by treating amino alcohol **4** with an acyl isocyanate, thus creating the required acidity in the imino hydrogen.

The ideal acyl isocyanate would balance this required imino acidity in the product with initial selective reaction at the secondary amine. With the highly reactive tosyl and trichloroacetyl isocyanates, this initial selectivity was absent; reaction occurred rapidly at both the secondary amino and primary hydroxyl groups. Aroyl isocyanates,[5] however, did react selectively at the amino group to form the aroyl ureas **10**.

The next step was to achieve ring closure by activating the primary hydroxyl group via the Mitsunobu reaction.[6] Studies on the mechanism of this reaction[7] have established that the acidic component acting as a nucleophile should have a $pK_a < 11$. The N–H bond of our aroyl ureas **10** fulfills this criterion, and indeed cyclization took place

(1) Sauerberg, P.; Chen, J.; WoldeMussie, E.; Rapoport, H. *J. Med. Chem.* **1989**, *32*, 1322.

(2) Although this reaction had previously[1] been described as giving a 32% yield of the *N*-CBZ derivative, we found the product to be mostly the *N,O*-bis-CBZ derivative.

(3) Sokolovsky, M.; Wilchek, M.; Patchornik, A. *J. Am. Chem. Soc.* **1964**, *86*, 1202.

(4) (a) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195. (b) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937. (c) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (d) Hata, T.; Yamamoto, I.; Sekine, M. *Chem. Lett.* **1975**, 977.

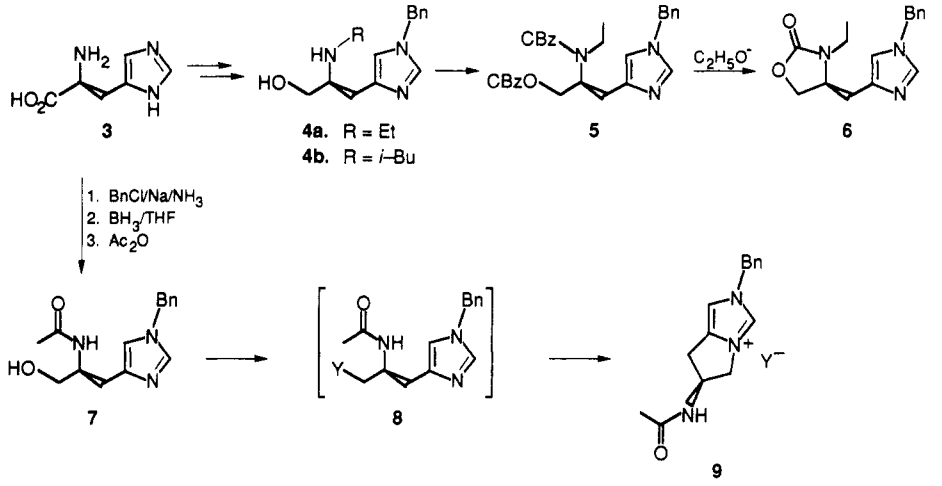
(5) Aromatic acyl isocyanates were prepared according to Caubere's procedure: Deng, M. Z.; Caubere, P.; Senet, J. P.; Lecolier, S. *Tetrahedron* **1988**, *44*, 6079. 4-Chlorobenzoyl isocyanate: 79% yield; bp 95–97 °C/1.5–2.0 mm (lit. bp 92–95 °C/2.0 mm); IR ($CHCl_3$) ν_{NCO} 2235 cm^{-1}. 2,4-Dichlorobenzoyl isocyanate: 82% yield; bp 110–113 °C/1.5–2.0 mm; IR ($CHCl_3$) ν_{NCO} 2230 cm^{-1}. 2-Chloro-4-nitrobenzoyl isocyanate: 78% yield; bp 143–146 °C/2.0 mm; IR ($CHCl_3$) ν_{NCO} 2135 cm^{-1}.

(6) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Castro, B. R. *Organic Reactions*; Wiley: New York, 1983; Vol. 29, p 1.

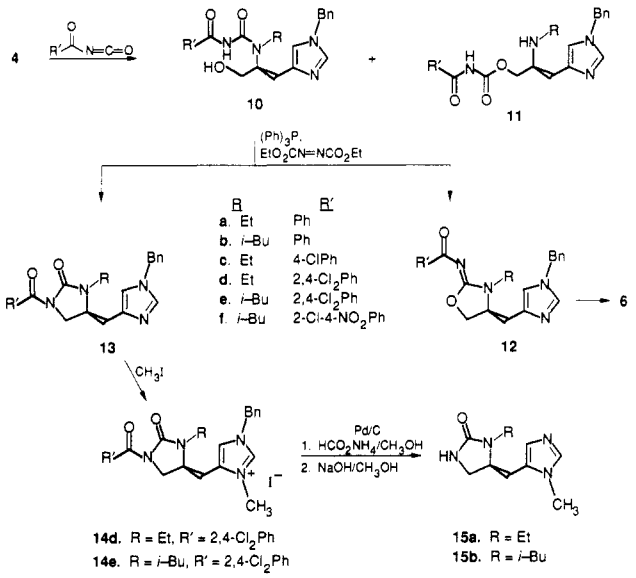
(7) (a) von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557. (b) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876. (c) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843. (d) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235. (e) Hughes, D. L.; Raemer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.

0022-3263/90/1955-3699$02.50/0

Scheme I



Scheme II



readily when these acyl ureas were exposed to diethyl azodicarboxylate and triphenylphosphine.

The problem was that this alkylation process led to mixtures of both O- and N-alkylated products, **12** and **13**, respectively. Since an increase in the N–H acidity was anticipated to increase the N- to O-alkylation ratio, this acidity was varied by changing the substitution pattern in the benzene ring. The most favorable ratio for N-alkylation (4/1) was obtained with 2,4-dichloro or 2-chloro-4-nitro substitution. These results are summarized in Table I. Increasing the electron-withdrawing groups in the aryl residue did give more N-alkylation; however, the increased reactivity in the isocyanate group led to decreased selectivity in the initial acylation. The best balance of both steps, selective reaction at the amino group and N-alkylation, resulted with 2,4-dichlorobenzoyl isocyanate.

The O- and N-cyclized products were easily separated. Hydrolysis of the O-alkylated product **12** gave the known oxazolidinone **6**. To prepare the target cyclic urea, the imidazole ring of the N-alkylated isomer **13** was methylated to the imidazolium iodide **14**. Transfer hydrogenolysis with ammonium formate/Pd–C then leads to debenzylation, and hydrolytic removal of the aroyl group gives the desired 2-imidazolidinone analogues **15a** and **15b** of pilocarpine in 72% and 75% yields from the initial N-alkylated products **13d** and **13e**, respectively.

This synthetic strategy successfully led to our target cyclic ureas. Furthermore, considering the nature of the transformations, one would expect such a process for converting a 1,2-amino alcohol into an imidazolidinone, and thence, by acid hydrolysis, into a 1,2-diamine, to be quite general.

Table I. Reaction of Histidinol 4 with Aroyl Isocyanates To Give Aroyl Ureas 10 and Cyclization of 10 to 2-Imidazolidinones 13 and 2-Oxazolidinones 12

	substituents		% yield of aroylurea 10	N-alkyl/O-alkyl[a] 13/12	% yield of 13[b]
	R	R'			
a	Et	Ph	86	56/44	50
b	*i*-Bu	Ph	73	59/41	51
c	Et	4-ClPh	80	57/43	*c*
d	Et	2,4-Cl_2Ph	76	80/20	75
e	*i*-Bu	2,4-Cl_2Ph	74	81/19	74
f	*i*-Bu	2-Cl-4-NO_2Ph	65	83/17	*c*

[a] The ratio of *N*- to *O*-alkylated products was determined by NMR analysis. [b] Isolated yield by column chromatography. [c] Not determined.

Experimental Section

General. Tetrahydrofuran (THF) was distilled immediately prior to use from sodium/benzophenone. Methanol was distilled from its magnesium salt. Acetone was decanted from 4A molecular sieves. Unless otherwise noted all nonaqueous reactions were carried out under a nitrogen atmosphere. Temperatures refer to bath temperatures. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Proton and carbon spectra were measured on a Bruker AM 400 or 500 spectrometer (in $CDCl_3$, unless otherwise indicated). Chemical shifts are reported downfield from TMS as internal standard, and coupling constants, *J*, are reported in hertz. Carbon multiplicities were determined by DEPT135 and DEPT90 experiments and are indicated as 3 (CH_3), 2 (CH_2), and 1 (CH). Chemical shifts for aromatic carbons are not reported. Elemental analyses were performed at the UC Berkeley Analytical Laboratory. Low-pressure chromatography (LPC) was performed using Kieselgel 60 (EM Science, 230–400 mesh) as the stationary phase.

(*S*)-3-Ethyl-4-[(1′-benzyl-4′-imidazolyl)methyl]-2-oxazolidinone (6). To a solution of *N,O*-bis-CBZ derivative **5** (0.25 g, 0.47 mmol)[2] in absolute ethanol (3 mL) was added ethanolic 2 N sodium ethoxide (0.6 mL). The reaction mixture was stirred for 7 min, acidified with 1 N hydrochloric acid (1 mL) and water (1 mL), and extracted into chloroform (15 mL). The organic phase was dried, filtered, and evaporated to give oxazolidione **6**, identical with an authentic sample.[1]

1-Benzyl-4-[2′-(acetylamino)-3′-hydroxypropyl]imidazole (7). Borane tetrahydrofuran complex (1.0 M solution in THF,

21 mL, 20.8 mmol) was slowly added to a suspension of 1-benzyl-L-histidine (3 g, 12.3 mmol)[1] in tetrahydrofuran (12 mL). The mixture was stirred for 15 h at room temperature and, after a further addition of borane tetrahydrofuran complex (21 mL, 20.8 mmol), was stirred an additional 15 h. The excess of borane was destroyed with ethanol, the mixture was acidified to pH 1 with 3 N hydrochloric acid, and the water was removed by azeotropic distillation with 2-propanol. Concentration to a small volume and dilution with ethyl acetate gave crystals which were filtered off, washed with ethyl acetate, and dried. The crystals were added to sodium (0.6 g) in absolute methanol (20 mL), the sodium chloride that formed was filtered off, and to the solution was added acetic anhydride (1.2 mL) at the room temperature. The mixture was stirred for 5 h at room temperature then evaporated. Recrystallization of the residue from toluene gave *N*-acetylamino alcohol **7**, 2.3 g, 69%: mp 153–154 °C; ^{1}H NMR δ 7.45 (s, 1 H), 7.39–6.85 (m, 5 H), 6.72 (s, 1 H), 5.04 (s, 2 H), 4.12–4.08 (m, 1 H), 3.73 (dd, 1 H, J = 11.5, 4.0), 3.56 (dd, 1 H, J = 11.5, 4.3), 2.88 (dd, 1 H, J = 14.8, 6.7), 2.79 (dd, 1 H, J = 14.6, 5.7), 1.92 (s, 3 H). Anal. Calcd for $C_{15}H_{19}N_3O_2$: C, 65.9; H, 7.0; N, 15.4. Found: C, 65.5; H, 7.0; N, 15.1.

***N*-Isobutyryl-1-benzyl-L-histidine Benzyl Ester.** 1-Benzyl-L-histidine benzyl ester di-*p*-toluenesulfonate (28.8 g, 42.4 mmol)[1] was added to saturated aqueous sodium bicarbonate, the pH was adjusted to 8 with sodium carbonate, and the mixture was extracted with chloroform/isopropyl alcohol, 4/1 (2 × 200 mL). The organic phase was dried, filtered, and evaporated, and the residue was stirred in pyridine (50 mL) with isobutyric anhydride (9.13 mL, 55.05 mmol) for 1 h. The solution was evaporated to a residue to which was added water, and the evaporation was repeated. The crude oily residue was dissolved in chloroform (300 mL), which was washed with saturated sodium bicarbonate solution (75 mL), dried, filtered, and evaporated. Recrystallization of the residue from toluene/petroleum ether gave ***N*-isobutyryl-1-benzyl-L-histidine benzyl ester**, 14.1 g, 82% yield, as white crystals: mp 68–69 °C; ^{1}H NMR δ 7.41 (d, 1 H, J = 1.2), 7.34–7.06 (m, 10 H), 6.35 (s, 1 H), 5.15–4.91 (m, 4 H), 4.84–4.80 (m, 1 H), 3.09–2.94 (m, 2 H), 2.47–2.40 (m, 1 H), 1.15 (d, 3 H, J = 6.9), 1.14 (d, 3 H, J = 6.9); ^{13}C NMR δ 176.77 (C=O), 171.19 (C=O), 66.42 (2), 52.00 (1), 50.51 (2), 35.20 (1), 29.20 (2), 19.23 (3). Anal. Calcd for $C_{24}H_{27}N_3O_3$: C, 71.1; H, 6.7; N, 10.4. Found: C, 71.1; H, 6.7; N, 10.4.

1-Benzyl-4-[2′-(isobutylamino)-3′-hydroxypropyl]-imidazole (4b). To a gently heated solution of lithium aluminum hydride (2.9 g, 76.4 mmol) in tetrahydrofuran (150 mL) was added a solution of ***N*-isobutyryl-1-benzyl-L-histidine benzyl ester** (10.4 g, 25.7 mmol) in tetrahydrofuran (50 mL). The reaction mixture was refluxed for 16 h and then cooled to room temperature. Water (50 mL) was added slowly, the mixture was stirred for 20 min at room temperature and filtered, and sodium chloride was added, causing separation of the aqueous phase, which was extracted with tetrahydrofuran (2 × 100 mL). The combined organic phases were dried, filtered, and evaporated to give an oil which crystalized from ether/toluene to give **4b**, 3.8 g, 52% yield: mp 93–94 °C; ^{1}H NMR δ 7.46 (d, 1 H, J = 1.2), 7.37–7.13 (m, 5 H), 6.68 (s, 1 H), 5.05 (s, 1 H), 3.61 (dd, 1 H, J = 10.8, 4.5), 3.39 (dd, 1 H, J = 10.8, 4.7), 2.92–2.87 (m, 1 H), 2.72–2.70 (m, 2 H), 2.43 (dd, 1 H, J = 11.3, 6.7), 2.37 (dd, 1 H, J = 11.3, 6.8), 1.70–1.60 (m, 1 H), 0.86 (d, 1 H, J = 6.6), 0.84 (d, 1 H, J = 6.6); ^{13}C NMR δ 62.87 (2), 58.45 (1), 54.96 (2), 50.75 (2), 30.67 (2), 28.63 (1), 20.57 (3). Anal. Calcd for $C_{17}H_{25}N_3O$: C, 71.0; H, 8.8; N, 14.6. Found: C, 70.9; H, 8.8; N, 14.5.

1-Benzoyl-3-ethyl-3-[1-(1′-benzyl-4′-imidazolyl)-3-hydroxyprop-2(*S*)-yl]urea (10a). 1-Benzyl-4-[2′-(ethylamino)-3′-hydroxypropyl]imidazole (**4a**) was prepared as reported.[1] A solution of benzoyl isocyanate (0.31 mL, 2.4 mmol) in tetrahydrofuran (5 mL) was added over 1 h via syringe pump to a solution of **4a** (0.57 g, 2.2 mmol) in tetrahydrofuran (15 mL) cooled in an ice bath. The reaction mixture was stirred for 1 h at room temperature and evaporated, and the crude product was purified by LPC with ethyl acetate/methanol, 9/1, as eluent to give **10a**, 0.78 g, 86% yield, as a white foam: ^{1}H NMR δ 7.96–7.25 (m, 11 H), 6.69 (s, 1 H), 4.99 (s, 2 H), 4.36–4.25 (br s, 1 H), 3.79–3.71 (m, 2 H), 3.40–3.18 (m, 2 H), 2.91–2.82 (m, 2 H), 1.03 (t, 3 H, J = 6.8).

1-Benzoyl-3-isobutyl-3-[1-(1′-benzyl-4′-imidazolyl)-3-hydroxyprop-2(*S*)-yl]urea (10b). As described for the preparation of **10a**, reaction of **4b** (0.21 g, 0.73 mmol) with benzoyl isocyanate gave **10b**, 0.21 g, 73% yield, as a white foam: ^{1}H NMR δ 7.96–7.05 (m, 11 H), 6.67 (s, 1 H), 5.00 (s, 2 H), 4.18–4.03 (br s, 1 H), 3.85–3.72 (m, 2 H), 3.28 (m, 2 H), 2.82–2.93 (m, 3 H), 1.93–1.81 (m, 1 H), 0.79 (d, 3 H, J = 6.1), 0.71 (d, 3 H, J = 5.8); ^{13}C NMR δ 166.76 (C=O), 154.52 (C=O), 63.39 (2), 50.69 (2), 27.92 (2), 27.03 (1), 20.05 (3).

1-(2,4-Dichlorobenzoyl)-3-ethyl-3-[1-(1′-benzyl-4′-imidazolyl)-3-hydroxyprop-2(*S*)-yl]urea (10d). As described for the preparation of **10a**, reaction of **4a** (0.5 g, 1.9 mmol) with 2,4-dichlorobenzoyl isocyanate (0.45 g, 2.1 mmol) gave **10d**, 0.7 g, 76% yield, as a white foam: ^{1}H NMR δ 7.36–7.26 (m, 9 H), 6.66 (s, 1 H), 4.91 (s, 2 H), 4.38–4.20 (br s, 1 H), 3.75–3.66 (m, 2 H), 3.32–3.10 (m, 2 H), 2.85–2.72 (m, 2 H), 1.20 (t, 3 H, J = 7.1); ^{13}C NMR δ 170.96 (C=O), 153.14 (C=O), 62.99 (2), 50.70 (2), 27.44 (2), 13.94 (3). Anal. Calcd for $C_{23}H_{24}Cl_2N_4O_3$: C, 58.1; H, 5.1; N, 11.8. Found: C, 58.0; H, 4.8; N, 11.6.

1-(2,4-Dichlorobenzoyl)-3-isobutyl-3-[1-(1′-benzyl-4′-imidazolyl)-3-hydroxyprop-2(*S*)-yl]urea (10e). As described for the preparation of **10a**, reaction of **4b** (0.5 g, 1.7 mmol) with 2,4-dichlorobenzoyl isocyanate (0.42 g, 1.9 mmol) gave **10e**, 0.66 g, 74% yield, as a white foam: ^{1}H NMR δ 7.35 (s, 1 H), 7.31–7.04 (m, 8 H), 6.62 (s, 1 H), 4.94 (s, 2 H), 4.05–3.85 (br s, 1 H), 3.75–3.68 (m, 2 H), 3.28–3.20 (m, 1 H), 3.00–2.91 (m, 1 H), 2.75–2.65 (m, 2 H), 1.83–1.75 (m, 1 H), 0.71 (d, 3 H, J = 6.1), 0.67 (d, 3 H, J = 5.8); ^{13}C NMR δ 63.33 (2), 50.85 (2), 27.70 (1), 26.99 (3), 19.98 (3). Anal. Calcd for $C_{25}H_{28}Cl_2N_4O_3$: C, 59.6; H, 5.6; N, 11.1. Found: C, 59.2; H, 5.3; N, 10.9.

1-(2-Chloro-4-nitrobenzoyl)-3-isobutyl-3-[1-(1′-benzyl-4′-imidazolyl)-3-hydroxyprop-2(*S*)-yl]urea (10f). As described for the preparation of **10a**, reaction of **4b** (0.1 g, 0.35 mmol) with 2-chloro-4-nitrobenzoyl isocyanate (0.09 g, 0.38 mmol) gave **10f**, 0.12 g, 65% yield, as a white foam: ^{1}H NMR δ 8.17–7.04 (m, 9 H), 6.63 (s, 1 H), 5.01 (s, 2 H), 4.00–3.75 (m, 3 H), 3.35–3.22 (m, 1 H), 3.30–3.05 (m, 1 H), 2.83–2.65 (m, 2 H), 1.86–1.76 (m, 1 H), 0.71 (t, 3 H, J = 5.9), 0.69 (t, 3 H, J = 5.8).

General Procedure for Cyclization of 10 to 13 and 12. To a stirred solution of **10** (1 mmol) and triphenylphosphine (0.34 g, 130 mol%) in tetrahydrofuran (13 mL) at room temperature was added a solution of diethyl azodicarboxylate (0.21 mL, 130 mol%) in tetrahydrofuran (5 mL). After being stirred for 2 h, the solution was evaporated and the residue was purified by LPC, eluting with ethyl acetate/methanol, 9/1, to give **13** (or with ethyl acetate for **13e**), followed by methanol to give **12**. The results are summarized in Table I.

(*S*)-1-Benzoyl-3-ethyl-4-[(1′-benzyl-4′-imidazolyl)-methyl]-2-imidazolidinone (13a) and 12a. 13a: yield, 50%; ^{1}H NMR δ 7.51–7.15 (m, 11 H), 6.75 (s, 1 H), 5.08 (s, 2 H), 4.13–4.10 (m, 1 H), 3.95 (dd, 1 H, J = 11.5, 8.8), 3.77 (dd, 1 H, J = 11.5, 7.3), 3.58 (dq, 1 H, J = 14.4, 7.3), 3.14 (dq, 1 H, J = 14.3, 8.6), 3.05 (dd, 1 H, J = 11.4, 3.8), 2.69 (dd, 1 H, J = 14.3, 8.6), 1.16 (t, 3 H, J = 7.2).

12a: yield, 32%; ^{1}H NMR δ 8.20 (s, 1 H), 8.18–7.13 (m, 10 H), 6.72 (s, 1 H), 5.06 (s, 2 H), 4.53 (t, 1 H, J = 8.6), 4.35 (dd, 1 H, J = 8.8, 5.9), 4.30–4.72 (m, 1 H), 3.85 (dq, 1 H, J = 14.2, 7.2), 3.33 (dq, 1 H, J = 14.1, 7.1), 3.08 (dd, 1 H, J = 14.3, 3.8), 2.74 (dd, 1 H, J = 14.5, 8.7), 1.28 (t, 3 H, J = 7.2).

(*S*)-1-Benzoyl-3-isobutyl-4-[(1′-benzyl-4′-imidazolyl)-methyl]-2-imidazolidinone (13b) and 12b. 13b: yield, 51%; ^{1}H NMR δ 7.66–7.11 (m, 11 H), 6.73 (s, 1 H), 5.03 (s, 2 H), 4.09–4.01 (m, 1 H), 3.93 (dd, 1 H, J = 10.8, 8.7), 3.78 (dd, 1 H, J = 11.4, 3.9), 3.30 (dd, 1 H, J = 13.9, 9.4), 2.99 (d, 1 H, J = 14.2), 2.88 (dd, 1 H, J = 14.0, 5.9), 2.68 (dd, 1 H, J = 14.3, 8.4), 2.00–1.93 (m, 1 H), 0.88 (d, 3 H, J = 6.6), 0.83 (d, 3 H, J = 6.6); ^{13}C NMR δ 170.15 (C=O), 154.06 (C=O), 51.33 (1), 50.72 (2), 48.62 (2), 45.96 (2), 31.10 (2), 26.29 (1), 20.10 (3), 19.61 (3).

12b: yield, 30%; ^{1}H NMR δ 8.18–7.11 (m, 11 H), 6.72 (d, 1 H, J = 1.0), 5.03 (s, 2 H), 4.52 (t, 1 H, J = 8.7), 4.37 (dd, 1 H, J = 9.0, 5.2), 4.29–4.21 (m, 1 H), 3.62 (dd, 1 H, J = 13.9, 9.1), 3.09–3.03 (m, 2 H), 2.72 (dd, 1 H, J = 14.4, 8.8), 2.15–2.05 (m, 1 H), 0.99 (d, 3 H, J = 6.7), 0.96 (d, 3 H, J = 6.7); ^{13}C NMR δ 174.61, 159.78, 70.59 (2), 55.51 (1), 50.82 (2), 50.07 (2), 30.38 (2), 26.48 (1), 20.05 (3), 19.82 (3).

(*S*)-1-(2,4-Dichlorobenzoyl)-3-ethyl-4-[(1′-benzyl-4′-imidazolyl)methyl]-2-imidazolidinone (13d) and 12d. 13d: yield, 75%; ^{1}H NMR δ 7.48 (d, 1 H, J = 0.9), 7.36–7.13 (m, 8 H),

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

A. K. S. Bhujanga Rao, C. Gundu Rao, and B. B. Singh*

R&D Centre, Reckitt & Colman of India Limited, Plot No. 176, SIPCOT Industrial Complex, Hosur 635 126, Tamilnadu, India

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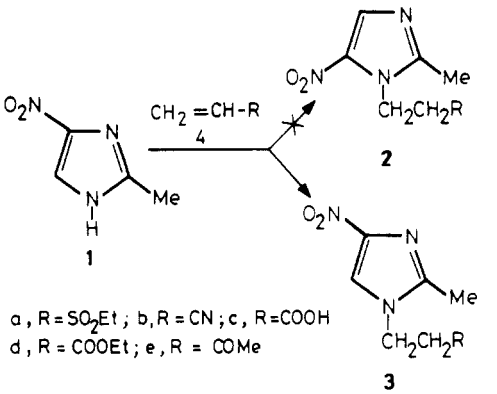
N-Substituted products from 2-methyl-4(5)-nitro-1*H*-imidazole (1) are of great utility as chemotherapeutic



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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