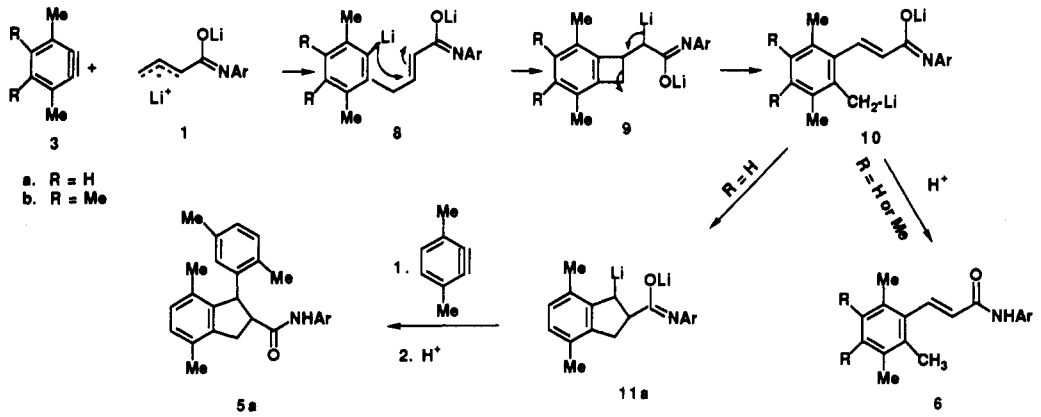
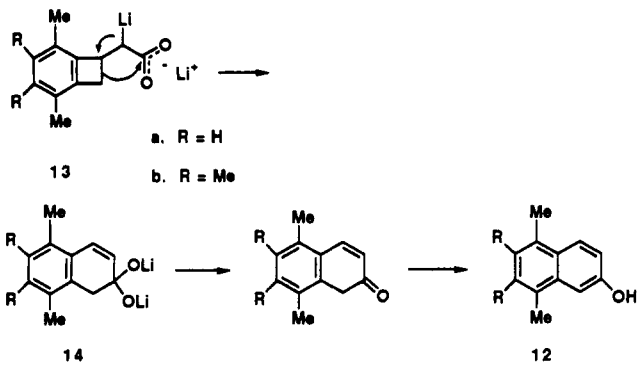
Scheme I



Scheme II



dianion intermediates proposed in these reactions.

Experimental Section

Melting points were determined on an electrothermal apparatus and are uncorrected. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (200 MHz) spectra were obtained in $CDCl_3$, and the chemical shifts were related to TMS. E. Merck silica gel 9385 (230–400 mesh) was used for flash chromatography. THF and *i*-Pr_2NH were obtained from Aldrich Chemical Co. and were thoroughly dried and distilled prior to use. Most of the other organic starting materials were also obtained from Aldrich Chemical Co. 2-Bromo-1,4-dimethyl benzene,[5c] 1-bromo-2,3,4,5-tetramethylbenzene,[5c] and *N*-(4-methoxyphenyl)-2-butenamide[1] were on hand from previous studies.

General Procedure for the Reaction of Dianions 1 and 2 with Arynes 3a,b. The reactions were carried in the usual way,[1] and the products were obtained in pure form by flash chromatography using a 5:95 mixture of acetone/hexane as eluent.

***N*-(4-Methoxyphenyl)-4,7-dimethyl-1-(2′5′-dimethylphenyl)indan-2-carboxamide (5a)**: yield 503 mg, 51%; mp 210–211 °C, ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3 H), 2.20 (s, 3 H), 2.32 (s, 3 H), 2.38 (s, 3 H), 3.10 (m, 1 H), 3.30 (s, 2 H), 4.9 (bd, 1 H), 6.8–7.1 (m, 7 H), 7.3 (d, 2 H, *J* = 8 Hz); IR ($CDCl_3$) 3428, 1681, 1598, 1513 cm^{-1}. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.16; H, 7.31, N, 3.50. Found: C, 81.31; H, 7.39; N, 3.45.

***N*-(4-Methoxyphenyl)-3-(2,3,4,5-pentamethylphenyl)-2-propenamide (6b)**: yield 178 mg, 55%; mp 237–238 °C; ^{13}C NMR ($CDCl_3$) δ 16.39, 16.77, 17.88, 55.42, 114.18, 121.72, 126.99, 131.20, 132.61, 133.04, 134.77, 135.80, 143.59, 156.56, 163.60; IR ($CHCl_3$) 34331, 1670, 1597, 1512 cm^{-1}. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67, H, 10.02, N, 5.57. Found: C, 71.98, H, 10.14, N, 5.75.

5,8-Dimethyl-2-naphthol (12a): yield 860 mg, 50%; mp 112–113 °C; ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3 H), 2.61 (s, 3 H), 5.07 (s, 1 H), 7.06–7.17 (m, 3 H), 7.29 (s, 1 H), 7.81 (d, 1 H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 19.31, 107.22, 116.71, 124.17, 126.76, 127.02, 128.14, 130.88, 132.35, 152.96; IR ($CHCl_3$) 3328, 1592, 1458 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.32. Found: C, 83.91; H, 7.39.

5,6,7,8-Tetramethyl-2-naphthol (12b): yield 18 mg, 8%; mp 115–117 °C; ^{1}H NMR δ 2.38 (s, 3 H), 2.40 (s, 3 H), 2.52 (s, 3 H), 2.58 (s, 3 H), 7.04 (d, 1 H, *J* = 9 Hz), 7.33 (d, 1 H, *J* = 2 Hz), 7.94 (d, 1 H, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 15.30, 17.08, 17.46, 106.96, 115.81, 126.36, 126.89, 127.30, 128.75, 130.65, 132.69, 133.77, 152.46; IR ($CHCl_3$) 3314, 1617, 1459 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.10; H, 8.39.

Acknowledgment. This work was supported in part by Grants from the Welch Foundation of Houston, TX, and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No. 1, 139409-00-0; 2, 83439-40-1; 3a, 59309-68-1; 3b, 76054-72-3; 5a, 139409-01-1; 6a, 139409-02-2; 6b, 139409-03-3; 12a, 102273-84-7; 12b, 139409-04-4; 2-chloro-1,4-dimethylbenzene, 95-72-7.

Supplementary Material Available: Positional coordinates, bond lengths, bond angles, and equivalent isotropic thermal parameters of non-hydrogen atoms of 5a as determined by X-ray crystallography (3 pages). Ordering information is given on any current masthead page.

Halogenation and Oxidation of 2,5-Bis(ethoxycarbonyl)-3,4-dialkylpyrroles. A Possible Route to Side-Chain Functionalized 3,4-Dialkylpyrroles

Enrico Baciocchi,* Ester Muraglia, and Giancarlo Sleiter*

Dipartimento di Chimica, Università "La Sapienza" and Centro CNR per lo Studio dei Meccanismi di Reazione, P.le A. Moro, 00185 Rome, Italy

Received September 16, 1991

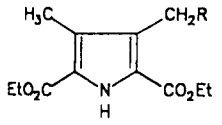
It is well-known that in the pyrrole nucleus, the reactivity of the α-position greatly exceeds that of the β-position, thus making the synthesis of β-substituted pyrroles an extremely difficult task, requiring the study and the development of particular synthetic procedures.[1] This situation also extends to side-chain reactivity; alkyl groups bonded to the α-position of the pyrrole nucleus are much more reactive than those bonded to the β-position. Thus, α-alkylpyrroles readily undergo oxidation,[2] halogenation,[3,4] aminoalkylation,[5] and isotope exchange[6] reactions. In

(1) Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.
(2) (a) Siedel, W.; Winkler, F. *Justus Liebigs Ann. Chem.* **1943**, *554*, 162. (b) Paine, J. B., III; Dolphin, D. *Can. J. Chem.* **1976**, *54*, 411. (c) Montforts, F.-P.; Schwartz, U. M. *Liebigs Ann. Chem.* **1985**, 2301.
(3) Angelini, G.; Illuminati, G.; Monaci, A.; Sleiter, G.; Speranza, M. *J. Am. Chem. Soc.* **1980**, *102*, 1377 and references therein.
(4) Angelini, G.; Giancaspro, C.; Illuminati, G.; Sleiter, G. *J. Org. Chem.* **1980**, *45*, 1786 and references therein.

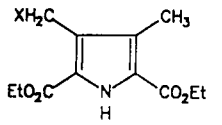
0022-3263/92/1957-2486$03.00/0

contrast, very few reactions involving direct attack on the β-alkyl side-chain have been described, despite the fact that β,β'-disubstituted pyrroles are extremely valuable for the synthesis of polypyrrolic systems, which, among other things, are of great interest as organic conductors. Accordingly, in 2,5-unsubstituted 3,4-dialkylpyrroles, alkyl-group functionalization is generally precluded by the high reactivity of the α-positions.[7]

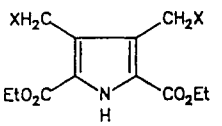
Recently, it was observed that the reaction of diethyl 3,4-dimethylpyrrole-2,5-dicarboxylate (**1a**) with Br_2 leads to good yields of the monobromo (**2a**) and dibromo (**3a**) derivatives.[8] Thus functionalization of a β-alkyl group can



1a (R=H)
1b (R=CH_3)



2a (X=Br)
2b (X=Cl)
2c (X=OAc)



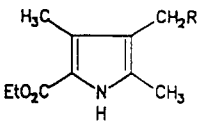
3a (X=Br)
3b (X=Cl)

be performed when the α-positions of the pyrrole nucleus are blocked by ethoxycarbonyl groups. It follows, in view of the possible hydrolytic/decarboxylative removal of the ester groups, that compounds like **1** may represent suitable substrates for the synthesis of side-chain functionalized 3,4-dialkylpyrroles.

In this paper, we report an improved procedure for the preparation of diesters **1** and document the side-chain reactions of these esters with halogenating and oxidizing agents. A preliminary study of the hydrolysis/decarboxylation process leading to side-chain functionalized 2,5-unsubstituted 3,4-dialkylpyrroles is also described.

Results

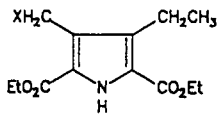
The key step in the synthesis of diesters **1** is the 5-CH_3 → 5-CO_2Et conversion of **4**, which is easily obtained from 3-alkyl-2,4-pentanedione and diethyl nitrosomalonate (see the Experimental Section). The usual procedure for this



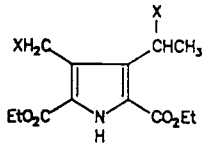
4a (R=H)
4b (R=CH_3)

conversion is perchlorination of the 5-methyl group followed by ethanolysis.[9] This method, however, turned out to be unsatisfactory for the preparation of large amounts of the diesters **1** required in the present work. Thus, a different approach to compounds **1** was chosen, consisting in the oxidation of **4** by $Pb(OAc)_4$ to give the corresponding 5-formyl derivatives,[2c] which were then converted into the desired diesters **1** by reaction with NaCN and MnO_2 in alcoholic medium.[10] This procedure, never before applied to methylpyrroles, afforded **1a,b** in about 45% overall yield.

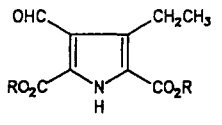
Bromination. With *N*-bromosuccinimide (NBS) in refluxing CCl_4 (benzoyl peroxide as promoter), bromination of diester **1a** led to a mixture of **2a** and **3a** (combined yield, 95%). Substantial amounts of **3a** were observed even when a significant excess of substrate (4:1) was used. With 2 equiv of NBS only the dibromo derivative **3a** was formed in a practically quantitative yield. In contrast, the diester **1b** reacted with 1 equiv of NBS to afford only the monobromo derivative **5a** (95%). No evidence for bromination of the ethyl group was obtained. With a 2-fold excess of NBS, the dibrominated diester **6a** is again formed in a practically quantitative yield. With both **1a** and **1b**, bromination products beyond the dibromination stage were not found.



5a (X=Br)
5b (X=Cl)
5c (X=OAc)



6a (X=Br)
6b (X=Cl)



7a (R=Et)
7b (R=H)

Br_2 (1 equiv) in CCl_4 at 70 °C behaves the same as NBS: with **1a** it always forms a mixture of **2a** and **3a**,[8] while with **1b** the monobromo derivative **5a** is exclusively produced. No bromination of the ethyl group is observed.

Chlorination. Four potential chlorinating agents were tested: sulfuryl chloride,[11] *N*-chlorosuccinimide (NCS), trichloroisocyanuric acid,[12] and phosphorus pentachloride.[13]

Sulfuryl chloride was unreactive toward both esters **1a** and **1b**, even in the presence of initiators such as azobisisobutyronitrile (AIBN) and benzoyl peroxide. NCS and trichloroisocyanuric acid reacted with **1a** and **1b**; however, chlorinated compounds on the β-side chain were not detected among the reaction products.

The only reagent that proved to be effective in producing β-(chloroalkyl)pyrroles was phosphorus pentachloride in chlorobenzene solvent at 110 °C. In contrast to the bromination process, from **1a** it was possible to obtain the monochlorinated product **2b**. Only traces of the dichloro derivative **3b** were detected, even when an excess of chlorinating agent was used. With diester **1b**, chlorination is, as bromination, regioselective, giving only the monochlorinated derivative **5b**.

Oxidation. The oxidation of the β-alkyl side chains was carried out using cerium(IV) ammonium nitrate (CAN)

(5) Curulli, A.; Sleiter, G. *J. Org. Chem.* **1985**, *50*, 4925. Curulli, A.; Giardi, M. T.; Sleiter, G. *Gazz. Chim. Ital.* **1983**, *113*, 115.
(6) Curulli, A.; Sleiter G. *Isotopenpraxis* **1983**, *19*, 207.
(7) Attempts to use the triisopropylsilyl group in position 1 to reduce the reactivity of the α-positions in 3,4-dialkylpyrroles have given unsatisfactory results in our laboratory.
(8) Cocco, D.; Giancaspro, C.; Sleiter, G. *Gazz. Chim. Ital.* **1981**, *111*, 145.
(9) Scarsella, M.; Sleiter, G. *Gazz. Chim. Ital.* **1988**, *118*, 757.
(10) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(11) Brown, H. C.; Ash, A. B. *J. Am. Chem. Soc.* **1955**, *77*, 4019.
(12) Juenge, E. C.; Beal, D. A.; Duncan, W. P. *J. Org. Chem.* **1970**, *35*, 719.
(13) Wyman, D. P.; Wang, J. Y. C.; Freeman, W. R. *J. Org. Chem.* **1963**, *28*, 3173.

which is known[14] to selectively oxidize the benzylic position of alkyl aromatic compounds. In acetic acid at 60 °C, both diesters **1a** and **1b** reacted cleanly, giving excellent yields (90%) of the β-acetoxymethyl derivatives **2c** and **5c**, respectively. Even in the presence of an excess of the oxidant and with prolonged reaction times, only one of the two alkyl groups is oxidized. Moreover, the reaction of **1b** involves only the methyl group; the ethyl group remains totally unaffected. When the reaction of **1b** with CAN was carried out in AcOH–H_2O (1:1) at 85 °C, diethyl 3-ethyl-4-formylpyrrole-2,5-dicarboxylate (**7a**) was obtained in 75% yield.

Decarboxylation. Since preliminary experiments showed that the side-chain halogenated diesters do not survive under the drastic reaction conditions generally used for the decarboxylation of pyrrolic carboxylate esters, we have so far investigated only the reaction of the formyl derivative **7a**. This compound was first hydrolyzed, by refluxing in ethanolic KOH, to the corresponding diacid **7b**. The latter was treated with copper chromite (barium promoted) in quinoline at 200 °C[15] to form 3-ethyl-4-formylpyrrole in 45% yield.

Discussion

The results presented here clearly indicate that diethyl 3,4-dialkylpyrrole-2,5-dicarboxylates are very suitable substrates for the side-chain reactions of β-alkyl groups. Both hydrogen atom transfer (HAT) and electron transfer (ET) reactions are possible as we note very efficient reactivity of **1a** and **1b** either with NBS (a bona fide HAT reagent)[16] in CCl_4 or with CAN (a genuine ET reagent)[17] in AcOH.

The observation that in the bromination of **1a** with NBS a mixture of the mono- and disubstituted products is always obtained, whereas clean monosubstitution occurs in the reaction of **1a** with CAN, is probably to be related to the different mechanism of the two reactions. Accordingly, our previous studies[18] have clearly shown that the intermolecular selectivity of the electron-transfer reaction promoted by CAN is much higher than that of HAT processes induced by NBS.

Another interesting observation is that in the reaction of **1b**, the reactivity of the ethyl group is much lower than that of the methyl group both in HAT (NBS and Br_2) and ET reactions. With NBS and Br_2, substitution at the ethyl group occurs only after the reaction at the methyl group is complete. Since an ethyl group is expected to be significantly more reactive than a methyl group in free radical reactions, we attribute these results to stereoelectronic effects. Molecular models of **1b** clearly show that the ethyl group, experiencing steric interactions with the adjacent ethoxycarbonyl and methyl groups, cannot assume a conformation in which the C_α–H bond is coplanar with the π-system. This situation strongly disfavors both hydrogen atom transfer and electron-transfer processes: the former, because no conjugative stabilization by the aromatic system of the incipient free radical is possible; the latter, because breaking of the C_α–H bond in the intermediate radical cation requires alignment with the π-system.[19] Recent studies have shown that stereoelectronic effects are more important in ET than in free radical reactions.[20] This can explain the observation that attack at the ethyl group *never* occurs when the reactant is CAN, but is possible with NBS and Br_2.

The reactions of **1a** and **1b** toward PCl_5 closely resemble the ones with CAN. Only monochlorination of **1a** is observed and attack at the ethyl group in **1b** never occurs. This finding may suggest the operation of an electron-transfer mechanism in the reaction induced by PCl_5. The chlorine radical, which should be the reactive species in the PCl_5-promoted chlorination,[13] is also a strong oxidant ($E°$ = 2.1 V vs NHE in MeCN),[21] significantly stronger than $Br^•$ (1.71 V vs NHE in MeCN[21]). Thus it is not unreasonable that reaction of PCl_5 with a relatively oxidizable substrate like **1a** or **1b** (E_p ca. 1.9 V vs NHE)[22] may occur by an ET mechanism.[23]

From the synthetic point of view, the above information is very useful as it indicates that NBS is to be the reagent of choice for the functionalization of both the alkyl groups of **1**, while CAN and PCl_5 are suitable reagents for monofunctionalization.

Finally, the satisfactory yield of 3-ethyl-4-formylpyrrole from the decarboxylation of **7b** may indicate that this methodology is suitable for the preparation of side-chain-substituted 3,4-dialkylpyrroles. Of course, also the side-chain-halogenated diesters might be useful in this respect, since the halogen can easily be replaced by groups which can better resist the experimental conditions for the decarboxylation process.

Experimental Section

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 80 MHz on a Bruker instrument in $CDCl_3$ solution unless otherwise indicated. Melting points are uncorrected. Merck silica gel 60 (70–230 mesh) was used for column chromatography. CCl_4 was dried over P_2O_5 and distilled. Mass spectra were obtained on a Hewlett-Packard 5970 mass selective detector, operating at 70 eV, coupled with a 5890 GC. Elemental analyses were performed by Dr. Tarli, CNR Laboratories of Montelibretti, Rome.

Ethyl 3,4,5-Trimethylpyrrole-2-carboxylate (4a). **4a** was prepared according to the procedure described in the literature[24] for ethyl 4-ethyl-3,5-dimethylpyrrole-2-carboxylate, starting from 3-methyl-2,4-pentanedione: mp 128 °C from 95% EtOH (lit.[25] mp 128 °C from 95% EtOH).

Ethyl 4-Ethyl-3,5-dimethylpyrrole-2-carboxylate (4b). **4b** was obtained according to the literature:[24] mp 90 °C from 95% EtOH (lit.[24] mp 90–91 °C from 95% EtOH); ^1H NMR δ (ppm) 1.03 (t, J = 7.6 Hz, 3 H, 4-CH_2CH_3), 1.33 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.18 (s, 3 H, 5-CH_3), 2.26 (s, 3 H, 3-CH_3), 2.36 (q, J = 7.6 Hz, 2 H, 4-CH_2CH_3), 4.28 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 8.85 (b s, 1 H, NH).

Ethyl 5-Formyl-3,4-dimethylpyrrole-2-carboxylate (8). **4a** was oxidized to **8** according to Montforts and Schwartz:[2c] mp 107–108 °C from MeOH (lit.[26] mp 108 °C from aqueous EtOH); ^1H NMR δ (ppm) 1.34 (t, J = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 2.22 (s,

(14) Syper, L. *Tetrahedron Lett.* **1966**, 4493.
(15) Anderson, H. J.; Clase, J. A.; Loader, C. E. *Synth. Commun.* **1987**, 401.
(16) Poutsma, L. A. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley: New York, 1973; Vol. II, Chapter 15.
(17) Baciocchi, E.; Mandolini, L.; Rol, C. *J. Am. Chem. Soc.* **1980**, *102*, 7597. Baciocchi, E.; Dalla Cort, A.; Eberson, L.; Mandolini, L.; Rol, C. *J. Org. Chem.* **1986**, *51*, 4544.
(18) Baciocchi, E.; Mandolini, L.; Rol, C. *Tetrahedron Lett.* **1976**, 3343.
(19) (a) Tolbert, L. M.; Khanna, R. K.; Popp, A. E.; Gelbaum, L.; Bottomley, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 2373. (b) Baciocchi, E.; Mattioli, M.; Romano, R.; Ruzziconi, R. *J. Org. Chem.*, in press.
(20) Baciocchi, E.; Mattioli, M.; Ruzziconi, R. *Tetrahedron Lett.*, in press.
(21) Eberson, L. *Adv. Phys. Org. Chem.* **1982**, *18*, 79.
(22) Tabba, H. D.; Smith, K. V. *J. Org. Chem.* **1984**, *49*, 1870.
(23) The existence of a mechanistic dichotomy (hydrogen atom transfer vs electron transfer pathway) is nowadays well recognized for the reactions of free radical species including halogen atoms, and we have recently found that even $Br^•$ can react by an ET mechanism, depending on the solvent and the substrate structure (Baciocchi, E.; Crescenzi, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 658).
(24) Kleinspehn, G. G. *J. Am. Chem. Soc.* **1955**, *77*, 1546.
(25) Fischer, H.; Walach, B. *Justus Liebigs Ann. Chem.* **1926**, *450*, 109.
(26) Fischer, H.; Hierneis, J. *Justus Liebigs Ann. Chem.* **1931**, *492*, 21.

3 H, 3-CH_3), 2.24 (s, 3 H, 4-CH_3), 4.32 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 9.74 (s, 1 H, CHO).

Ethyl 4-Ethyl-5-formyl-3-methylpyrrole-2-carboxylate (9). 9 was prepared as described for 8, starting from **4b**, and purified by recrystallization from MeOH–petroleum ether (bp 40–70 °C): mp 91–91.5 °C (lit.[28] mp 90 °C from water); ^{1}H NMR δ (ppm) 1.07–1.43 (m, 6 H, 4-CH_2CH_3 and $CO_2CH_2CH_3$), 2.25 (s, 3 H, 3-CH_3), 2.71 (q, J = 7.6 Hz, 2 H, 4-CH_2CH_3), 4.32 (q, J = 7.1 Hz, 2 H, $CO_2CH_2CH_3$), 9.74 (s, 1 H, CHO).

Diethyl 3,4-Dimethylpyrrole-2,5-dicarboxylate (1a). A mixture of 8 (7.7 mmol), activated manganese dioxide (Aldrich) (157 mmol), sodium cyanide (40 mmol), and glacial acetic acid (0.69 mL, 12 mmol) in 120 mL of absolute ethanol was stirred at room temperature overnight. After concentration under reduced pressure, brine was added and the suspension was extracted several times with diethyl ether. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and then with brine and dried over Na_2SO_4, and the solvent was removed by evaporation under reduced pressure. The brown solid residue, after column chromatography (SiO_2, diethyl ether–hexane, 1:1), afforded 1.276 g (70%) of **1a**, which was recystallized from cyclohexane, mp 70 °C (lit.[27] mp 69–70 °C from EtOH).

Diethyl 3-Ethyl-4-methylpyrrole-2,5-dicarboxylate (1b). The title compound was obtained from **9** (0.069 mol), activated MnO_2 (Aldrich) (1.45 mol), NaCN (0.37 mol), and glacial AcOH (6.2 mL, 0.11 mol) as described above for **1a**. Yield (after chromatography, SiO_2, diethyl ether–hexane, 1:1) 12.6 g (72%). **1b** melted at 51–51.5 °C after recrystallization from aqueous EtOH (lit.[28] mp 50 °C from the same solvent): ^{1}H NMR δ (ppm) 1.07 (t, J = 7.5 Hz, 3 H, 3-CH_2CH_3), 1.34 (t, J = 7.1 Hz, 6 H, 2 $CO_2CH_2CH_3$), 2.25 (s, 3 H, 4-CH_3), 2.72 (q, J = 7.5 Hz, 2 H, 3-CH_2CH_3), 4.32 (q, J = 7.1 Hz, 4 H, 2 $CO_2CH_2CH_3$), 9.35 (b s, 1 H, NH).

Diethyl 3,4-Bis(bromomethyl)pyrrole-2,5-dicarboxylate (3a). A mixture of **1a** (0.80 mmol), NBS (0.175 mmol), and benzoyl peroxide as promoter in 8.5 mL of dry CCl_4 was stirred under reflux for 2 h. The succinimide formed was filtered, and the filtrate was evaporated to dryness under reduced pressure to afford a white solid (0.300 g, 95%), which was recrystallized from cyclohexane (mp 141.5–142.5 °C) [lit.[8] mp 141.5–142.3 °C from CCl_4–petroleum ether (bp 40–70 °C)].

Diethyl 3-(Bromomethyl)-4-ethylpyrrole-2,5-dicarboxylate (5a). A mixture of **1b** (1.97 mmol), NBS (2.10 mmol), and benzoyl peroxide as promoter in 20 mL of dry CCl_4 was stirred under reflux for 3 h. The workup was as described above for **3a**. A yellow oily residue (0.620 g, 95%) was obtained which turned solid after some days and was recrystallized from cyclohexane: mp 91–92 °C; ^{1}H NMR δ (ppm) 1.19 (t, J = 7.5 Hz, 3 H, 4-CH_2CH_3), 1.36 (t, J = 7.1 Hz, 3 H, 5-$CO_2CH_2CH_3$), 1.39 (t, J = 7.1 Hz, 3 H, 2-$CO_2CH_2CH_3$), 2.81 (q, J = 7.5 Hz, 2 H, 4-CH_2CH_3), 4.34 (q, J = 7.1 Hz, 2 H, 5-$CO_2CH_2CH_3$), 4.38 (q, J = 7.1 Hz, 2 H, 2-$CO_2CH_2CH_3$), 4.73 (s, 2 H, 3-CH_2Br), 9.66 (b s, 1 H, NH). Anal. Found for $C_{13}H_{18}BrNO_4$ (Calcd): C, 46.5 (47.0); H, 5.5 (5.5); N 4.2 (4.2).

Diethyl 3-(1-Bromoethyl)-4-(bromomethyl)pyrrole-2,5-dicarboxylate (6a). A mixture of **1b** (1.97 mmol), NBS (4.20 mmol), and benzoyl peroxide as promoter in 20 mL of dry CCl_4 was reacted as described above for the preparation of **5a**, yielding a yellow oily residue (0.800 g; 99%): ^{1}H NMR δ (ppm) 1.39 (2 t, $J_1 = J_2$ = 7.1 Hz, 6 H, 2 $CO_2CH_2CH_3$), 2.13 (d, J = 7.2 Hz, 3 H, CH_3, 1-bromoethyl), 4.39 (2 q, $J_1 = J_2$ = 7.1 Hz, 4 H, 2 $CO_2CH_2CH_3$), 4.98 (app. s, 2 H, CH_2Br), 6.12 (app. q, J = 7.2 Hz, 1 H, CHBr, 1-bromoethyl), 9.65 (b s, 1 H, NH). **6a** was further characterized as the diol **10** (see below).

Diethyl 3-(1-Hydroxyethyl)-4-(hydroxymethyl)pyrrole-2,5-dicarboxylate (10). A solution of **6a** (4.4 mmol) in 2.0 mL of acetone was added in one portion to a stirred suspension of potassium carbonate (22 mmol) in 4.0 mL of water and 8.0 mL of acetone. Water was then added, and the mixture was extracted three times with chloroform. The combined organic phases were washed with brine and dried over Na_2SO_4, and the solvent was removed by evaporation under reduced pressure. The white solid residue was filtered through silica gel using diethyl ether as eluent to afford 0.119 g (95%) of **10**: mp 88.5–90 °C from benzene–cyclohexane; ^{1}H NMR δ (ppm) 1.27–1.52 (m, 9 H, 2 $CO_2CH_2CH_3$ and CH_3 of 1-hydroxyethyl), 3.9 (b s, 2 H, 2 OH), 4.36 (q, J = 7.1 Hz, 4 H, 2 $CO_2CH_2CH_3$), 4.83 (d, J = 4.3 Hz, 2 H, CH_2 of 4-hydroxymethyl), 5.32 (q, J = 6.6 Hz, 1 H, CH of 1-hydroxyethyl); 9.56 (b s, 1 H, NH). Anal. Found for $C_{13}H_{19}NO_6$ (Calcd): C, 54.36 (54.73); H, 6.75 (6.71); N, 4.83 (4.91).

Diethyl 3-(Chloromethyl)-4-methylpyrrole-2,5-dicarboxylate (2b). A mixture of **1a** (0.8 mmol) and phosphorus pentachloride (1.4 mmol) in 10 mL of chlorobenzene was stirred under nitrogen at 110 °C for 48 h. After cooling, the resulting clear light yellow solution was distilled under reduced pressure. In order to remove any residual chlorobenzene, the residue was taken up with 20 mL of petroleum ether (bp 80–100 °C) which was then distilled off under reduced pressure. This procedure was repeated three times. Finally, petroleum ether (bp 40–70 °C) was added and the solution was left at −10 °C for 3 h. The white crystals that formed were collected and washed with cold petroleum ether (bp 30–50 °C) to afford 0.207 g (95%) of **2b** that showed the presence of a trace of **3b** (by NMR): ^{1}H NMR δ (ppm) 1.36 (t, J = 7.1 Hz, 3 H, 5-$CO_2CH_2CH_3$), 1.38 (t, J = 7.1 Hz, 3 H, 2-$CO_2CH_2CH_3$), 2.35 (s, 3 H, 4-CH_3), 4.34 (q, J = 7.1 Hz, 2 H, 5-$CO_2CH_2CH_3$), 4.37 (q, J = 7.1 Hz, 2 H, 2-$CO_2CH_2CH_3$), 4.82 (s, 2 H, CH_2Cl), 9.55 (b s, 1 H, NH). The spectrum shows also a weak signal at δ 4.93 (s), attributable to the two CH_2Cl groups of **3b**. **2b** was characterized as the acetate **2c** (method B).

Diethyl 3-(Acetoxymethyl)-4-methylpyrrole-2,5-dicarboxylate (2c). Method A. **1a** (1.6 mmol) was added in one portion under nitrogen to a stirred suspension of CAN (5.4 mmol) in 88 mL of glacial acetic acid at 60 °C. After 3 h the reaction was over, brine was then added, and the mixture was extracted three times with chloroform. The combined organic phases were washed with brine, a saturated solution of $NaHCO_3$, and brine again and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The pale yellow solid residue, after column chromatography (SiO_2, diethyl ether–hexane, 1:2), afforded 0.403 g of **2c** (85%) as a white solid: mp 90–91 °C (from aqueous ethanol). **Method B:** 200 mg of crude **2b** was added to 10 mL of a saturated solution of sodium acetate in glacial acetic acid. The solution was diluted with 50 mL of brine and extracted three times with chloroform. The combined organic phases were washed with brine and dried over Na_2SO_4, and the solvent was removed by evaporation under reduced pressure. The white solid residue was purified by column chromatography (SiO_2, diethyl ether–hexane, 1:2) to afford 0.201 g of **2c**: ^{1}H NMR δ (ppm) 1.29 (app. t, J = 7.1 Hz, 6 H, 2 $CO_2CH_2CH_3$), 2.01 (s, 3 H, 4-CH_3), 2.31 (s, 3 H, CH_3CO), 4.33 (q, J = 7.1 Hz, 4 H, 2 $CO_2CH_2CH_3$), 5.26 (s, 2 H, CH_2OAc), 9.66 (b s, 1 H, NH). Anal. Found for $C_{14}H_{19}NO_6$ (Calcd): C, 56.9 (56.56); H, 6.6 (6.44); N, 4.8 (4.71).

Diethyl 3-(Chloromethyl)-4-ethylpyrrole-2,5-dicarboxylate (5b). A mixture of **1b** (1.6 mmol) and phosphorus pentachloride (2.9 mmol) in 20 mL of chlorobenzene was reacted as described above for **2b**. After the same workup, 0.350 g (93%) of **5b** was obtained, which was recrystallized from petroleum ether (bp 40–70 °C) mp 87–88 °C; ^{1}H NMR δ (ppm) 1.08–1.46 (m, 9 H, 2 $CO_2CH_2CH_3$ and 4-CH_2CH_3), 2.80 (q, J = 7.5 Hz, 2 H, 4-CH_2CH_3), 4.34 (q, J = 7.1 Hz, 2 H, 5-$CO_2CH_2CH_3$), 4.37 (q, J = 7.1 Hz, 2 H, 2-$CO_2CH_2CH_3$), 4.81 (s, 2 H, CH_2Cl), 9.63 (b s, 1 H, NH). Anal. Found for $C_{13}H_{18}NO_4$ (Calcd): C, 54.5 (54.3); H, 6.3 (6.3); N, 4.8 (4.9).

Diethyl 3-(Acetoxymethyl)-4-ethylpyrrole-2,5-dicarboxylate (5c). According to the procedure reported for **2c** (method A), 1.9 mmol of **1b** afforded 0.531 g of **5c** (90%) as a white solid: mp 70.5–72 °C (from aqueous ethanol); ^{1}H NMR δ (ppm) 1.10 (t, J = 7.5 Hz, 3 H, 4-CH_2CH_3), 1.33 (t, J = 7.1 Hz, 3 H, 5-$CO_2CH_2CH_3$), 1.34 (t, J = 7.1 Hz, 3 H, 2-$CO_2CH_2CH_3$), 2.01 (s, 3 H, CH_3CO), 2.76 (q, J = 7.5 Hz, 2 H, 4-CH_2CH_3), 4.33 (q, J = 7.1 Hz, 4 H, 2 $CO_2CH_2CH_3$), 5.25 (s, 2 H, 3-CH_2OAc), 9.63 (b s, 1 H, NH). Anal. Found for $C_{15}H_{21}NO_6$ (Calcd): C, 57.01 (56.87); H, 6.78 (6.80); N, 4.37 (4.50).

Diethyl 3-Ethyl-4-formylpyrrole-2,5-dicarboxylate (7a). To a stirred solution of CAN (25 mmol) in aqueous 50% (v/v) AcOH (225 mL) was added **1b** (6 mmol). After 1 h at 85 °C, the mixture was diluted with water, extracted with diethyl ether,

(27) Eisner, U.; Linstead, R. P.; Parkes, E. A.; Stephen, E. *J. Chem. Soc.* **1956**, 1655.

(28) Fischer, H.; Siedel, W.; Le Thierry d'Ennequin, L. *Justus Liebigs Ann. Chem.* **1933**, *500*, 137.

washed with brine, and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography (SiO_2, diethyl ether–hexane, 1:1) gave 1.20 g of **7a** (75%), which was recrystallized from hexane: mp 94–95 °C; ^1H NMR δ (ppm) 1.13 (t, J = 7.4 Hz, 3 H, 3-CH_2CH_3), 1.37 (t, J = 7.1 Hz, 3 H, 2-$CO_2CH_2CH_3$), 1.39 (t, J = 7.1 Hz, 3 H, 5-$CO_2CH_2CH_3$), 3.11 (q, J = 7.4 Hz, 2 H, 3-CH_2CH_3), 4.37 (q, J = 7.1 Hz, 2 H, 2-$CO_2CH_2CH_3$), 9.7 (b s, 1 H, NH), 10.54 (s, 1 H, CHO). Anal. Found for $C_{13}H_{17}NO_5$ (Calcd) C, 58.37 (58.42); H, 6.41 (6.41); N, 5.14 (5.24).

3-Ethyl-4-formylpyrrole-2,5-dicarboxylic Acid (7b). A mixture of **7a** (3.7 mmol) in a 2 N solution of KOH in 90% (v/v) aqueous EtOH (33 mL) was refluxed for 5 h. The mixture was then poured onto ice, acidified with 10% H_2SO_4, extracted with chloroform, washed with brine, and dried over Na_2SO_4 to afford **7b** as a white solid (88%), which was recrystallized from glacial AcOH: mp 226 °C dec; ^1H NMR (acetone-d_6) δ (ppm) 1.19 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 3.17 (q, J = 7.4 Hz, 2 H, CH_2CH_3), 7.85 (b s, 2 H, 2 CO_2H), 10.36 (s, 1 H, CHO), 11.45 (b s, 1 H, NH). Anal. Found for $C_9H_9NO_5$ (Calcd): C, 51.24 (51.19); H, 4.25 (4.30); N, 6.63 (6.63).

3-Ethyl-4-formylpyrrole. The decarboxylation of **7b** was achieved according to the procedure of Anderson.[15] To a stirred suspension of copper chromite barium promoted (Aldrich) (0.345 g) in quinoline (10 mL) at 200 °C (internal temperature) was added **7b** (1.9 mmol). After 10 min carbon dioxide evolution ceased; the dark oil was poured onto ice, and concd HCl (8 mL) was added while stirring. The solid was filtered, and the filtrate was extracted several times with diethyl ether. The combined organic phases were washed with a saturated solution of $NaHCO_3$ and then brine and dried over Na_2SO_4. Evaporation of the solvent afforded 45% of 3-ethyl-4-formylpyrrole as a yellow oil which turned brown quickly: ^1H NMR δ (ppm) 1.20 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 2.75 (q, J = 7.3 Hz, 2 H, CH_2CH_3), 6.55–6.58 (m, 1 H, 2-H pyrrole), 7.29–7.33 (m, 1 H, 5-H pyrrole), 9.83 (d, J = 0.5 Hz, 1 H, CHO); mass spectrum, m/z (relative intensity) 123 (M^+, 100), 108 (86), 94 (M^+ – CHO, 45), 53 (44). The instability of the product did not allow us to obtain a satisfactory elemental analysis.

Acknowledgment. This work was supported by the CNR Progetto Finalizzato Chimica Fine II.

Registry No. **1a**, 2199-55-5; **1b**, 7467-77-8; **2b**, 139070-42-1; **2c**, 139070-43-2; **3a**, 78633-82-6; **4a**, 2199-46-4; **4b**, 2199-47-5; **5a**, 139070-44-3; **5b**, 139070-45-4; **5c**, 139070-46-5; **6a**, 139070-47-6; **7a**, 139070-48-7; **7b**, 139070-49-8; **8**, 4391-99-5; **9**, 4391-87-1; **10**, 139070-50-1; 3-ethyl-4-formylpyrrole, 139070-51-2.

Supplementary Material Available: ^1H NMR spectrum of 3-ethyl-4-formylpyrrole (1 page). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Novel and Convenient Route to 3′-Carbonates from Unprotected 2′-Deoxynucleosides through an Enzymatic Reaction

Franciso Moris and Vicente Gotor*

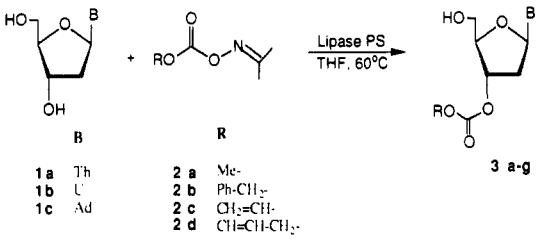
Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, Oviedo 33071, Spain

Received September 25, 1991

Introduction

2′-Deoxynucleosides have attracted much attention as potential antiviral agents,[1] and the usefulness of nucleosides modified in the 3′-position has led to a rising interest in the development of procedures for their preparation.

Scheme I



The primary hydroxyl group has had to be protected to obtain such derivatives.

Regioselective acylation of the 3′-hydroxyl group of nucleosides is a difficult reaction by conventional methods. Only through enzymatic reactions can it be achieved.[2] Recently, we have found that the reaction of pyrimidine and purine 2′-deoxynucleosides with oxime esters and lipase PS in pyridine is a versatile method to prepare 3′-O-acylated derivatives.[3] Given this set of circumstances, we are able to report, to the very best of our knowledge, on the first procedure for the regioselective synthesis of 3′-carbonates from the unprotected nucleosides. These compounds play an important role in the synthesis of oligonucleotides and other derivatives (such as dinucleoside carbonates). For example, the benzyloxycarbonyl group (Cbz) is commonly introduced using benzyl chloroformate;[4] however, this reaction does not allow direct preparation of the 3′-*O*-carbonate because substitution takes place preferably on the primary hydroxyl group.[4,5]

Results and Discussion

One approach to this problem involves using an appropriate reagent for alkoxycarbonylation. We thought of two possibilities: either acetone *O*-[(alkyloxy)carbonyl]oximes **2** or pyrocarbonates, the latter because of their analogy with anhydrides, which have been used in acylations of 2′-deoxynucleosides.[2] These nucleosides, when tested with pyrocarbonates under the same conditions, gave a complex mixture of compounds. Moreover, only dialkyl pyrocarbonates are commercially available; others, such as dibenzyl pyrocarbonate have been prepared[6] but are compounds with proven instability.

On the other hand, acetone *O*-[(alkyloxy)carbonyl]-oximes **2**, are similar to oxime esters (useful acylating agents in enzymatic reactions),[3,8] and their behavior in enzymatic alkoxycarbonylations has not been tested, a fact that prompted us to carry out this reaction with compounds **2**. Stability and availability (from the corresponding chloroformates) are additional advantageous features of these compounds which, except for **2b**,[7] have not been described in the literature (for physical and spectral data see Table II).

After a preliminary screening to find the most desirable enzyme and reaction conditions, we selected lipase Amano PS as a catalyst and tetrahydrofuran as a solvent (Scheme I). Other solvents, such as pyridine, DMSO, or DMF were not as effective as THF; however, 1,4-dioxane can be used as an alternative to THF. This reaction did not take place

(1) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17. de Clercq, E. *Tr. Pharm. Sci.* **1987**, *8*, 339.

(2) Nozaki, K.; Uemura, A.; Yamashita, I.; Yasumoto, M. *Tetrahedron Lett.* **1990**, *31*, 7327.

(3) Gotor, V.; Moris, F. *Synthesis*, in press.

(4) Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471.

(5) Lestinger, R. L.; Ogilvie, K. K. *J. Org. Chem.* **1967**, *32*, 296. Cook, A. F. *J. Org. Chem.* **1968**, *33*, 3589.

(6) Allainmat, M.; Plusquellec, D. *Tetrahedron Lett.* **1991**, *32*, 2751.

(7) Fernández, S.; Menéndez, E.; Gotor, V. *Synthesis* **1991**, 713.

(8) Ghogare, A.; Kumar, G. S. *J. Chem. Soc., Chem. Commun.* **1989**, 1533. Ghogare, A.; Kumar, G. S. *J. Chem. Soc., Chem. Commun.* **1990**, 134. Gotor, V.; Pulido, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 491.

0022-3263/92/1957-2490$03.00/0