Radical-based syntheses of 5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-a]pyrrole-1-carboxylic acid (ketorolac)[1]

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Short, efficient, and convergent syntheses of ketorolac (**1**) based on the inter- or intramolecular oxidative addition of malonyl and substituted malonyl radicals to 2-benzoylpyrrole and derivatives thereof are described.

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On décrit des synthèses à la fois courtes, efficaces et convergentes du kétorolac **1** qui sont basées sur l'addition oxydante inter- ou intra-moléculaire de radicaux malonyles ou malonyles substitués sur le 2-benzoylpyrrole et ses dérivés.

[Traduit par la rédaction]

Ketorolac (5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (**1**, Scheme 1) is a powerful non-narcotic analgesic that is used clinically for the management of moderate to severe pain states (1). Both linear (2) and convergent (3, 4) syntheses of this compound, and its derivatives, based on "ionic" bond formation processes have been reported. This paper describes new synthetic approaches to ketorolac in which the salient feature is the oxidative addition of an "electrophilic" radical species to a 2-benzoylpyrrole derivative.

Malonate anions of type **2** (X = Cl, Br, SO_2Me) readily cyclize to the bicyclic esters **3** and consequently they are valuable intermediates in the synthesis of ketorolac and congeners thereof (3, 4). It seemed to us that the alkylmalonyl radical **4** might add intramolecularly to the relatively electron-rich pyrrole nucleus to give the bicyclic radical **5**, which on oxidation to the cationic species **6** and proton loss therefrom would provide another route to the diester **3**. The recently described manganese(III) acetate induced cyclizations of β-arylethyl-, λ-arylpropyl-, β-aryloxyethyl-, and λ-aryloxypropylmalonates are the first reported examples of just such a process (5).

To ascertain if ketorolac could indeed be obtained by an oxidative radical cyclization process, the known (6) *N*-chloroethylpyrrole **7** (Scheme 2) was converted into the corresponding solvolytically sensitive iodide **8** (sodium iodide in boiling acetonitrile), which was immediately reacted with the sodium salt of diethyl malonate in dimethylformamide (DMF) solution. Reaction of the alkylmalonate **9** thus obtained with 2.5 equivalents of manganese(III) acetate (generated *in situ* from $Mn(OAc)_2 \cdot 4H_2O$),[4] in acetic acid solution at 80°C, gave the cyclic diester **11** in nearly quantitative yield. The amount of Mn(III) could be reduced by 60%, without a diminution in the yield of **11**, by using sodium persulfate (in the presence of Ag(I) as a cocatalyst) to reoxidize Mn(II) to Mn(III) (8). This result indicates that the latter process might well be made catalytic in Mn(III) but this possibility was not examined. Saponification of **11** and decarboxylation of the diacid gave ketorolac (**1**) in over 50% yield based on 2-benzoylpyrrole, the immediate precursor of **7**.

The conversion of **9** to **11** could also be effected by abstraction of Br· from the bromomalonate **10** mediated by the aerial oxidation of triethylborane (9, 10). The nature of the specie(s) responsible for the transformation of the bicyclic radical (i.e., corresponding to **5**) to **11** is not known. Compound **10** was synthesized by bromination of the sodium salt of **9** with *N*-bromosuccinimide.

It was of considerable interest to determine if diethyl 5-benzoylpyrrole-2-malonate (**14**, Scheme 3) could be synthesized by the reaction of the diethyl malonyl radical with 2-benzoylpyrrole (**12**). Compound **14** is of obvious synthetic importance because base-induced alkylation with an appropriate 1,2-disubstituted ethane derivative would most certainly produce the bicyclic ester **11**.

The Mn(III)-induced reaction of diethyl malonate with 2-benzoylpyrrole gave the α-acetoxy derivative **13** as the major product. The formation of this substance was not unexpected (11) nor was it prevented by the use of diethyl chloromalonate, a stratagem that has been utilized to obviate such overoxidation (12, 13). The desired malonate **14** could be obtained from **13**, albeit in modest yield, by triethylsilane – trifluoracetic acid reduction. Compound **14** could, however, be directly prepared from 2-benzoylpyrrole in excellent yield (86%) when the diethyl malonyl radical was generated from diethyl bromomalonate by the triethylborane-autoxidation process.

As expected, potassium carbonate induced alkylation of **14** with 1,2-dichloroethane (reactant and solvent), in the presence of 1 equivalent of tetra-*n*-butylammonium bromide, gave the bicyclic ester **11** in ca. 70% yield.

We have recently shown (14) that electron-rich aromatic systems undergo Mn(III)-induced tri(ethoxycarbonyl)methylation with triethyl methanetricarboxylate and that the triester **15** is formed as the only product (86%) from 2-benzoylpyrrole. The dealkoxycarbonylation of trialkyl alkane-1,1,1-tricarboxylates under basic conditions is known to be facile (15) and the conversion of **15** to **14** could be efficiently effected with sodium ethoxide in DMF at room temperature. Thus, this process not only constitutes a simple solution to the overoxidation problem, it also means that **15** is functionally equivalent to the malonate ester **14**. Indeed, reaction of **15** with 1,2-dichloroethane under conditions identical to those used with **14** gave the bicyclic diester **11**

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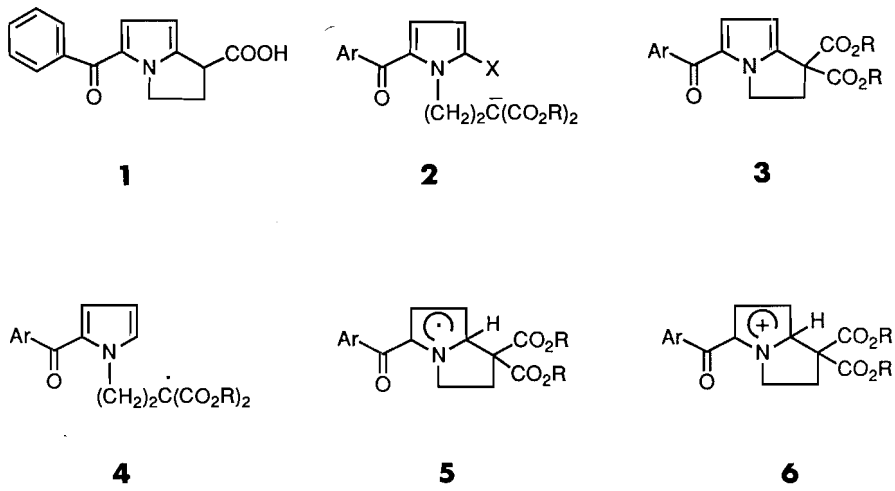
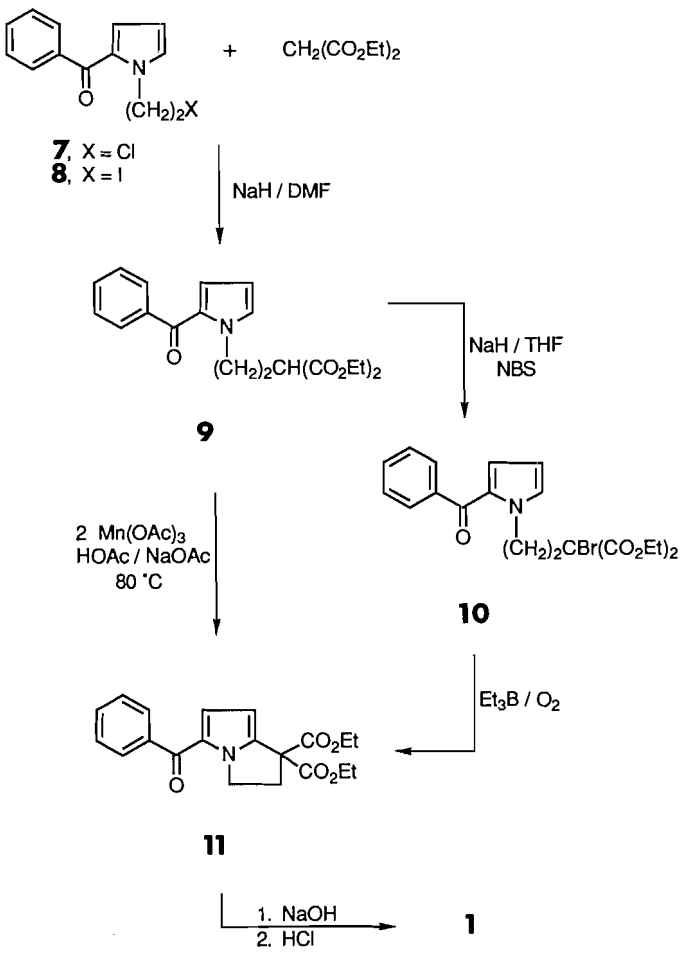
[4]$KMnO_4$ was used as the oxidant (7). This method obviates the need to purchase the costly Mn(III) reagent.



SCHEME 1



SCHEME 2

directly in 80% yield. This, therefore, is the shortest and most efficient (64% overall yield from 2-benzoylpyrrole) synthesis of ketorolac published to date.

The regiospecificity of the reaction of the diethyl malonyl, diethyl chloromalonyl, and tri(ethoxycarbonyl)methyl radicals with 2-benzoylpyrrole is especially noteworthy. The outcome of these reactions can be accounted for on the basis of the principles of the Frontier Molecular Orbital Theory, the regiospecificity being related to the relative values of the squares of the coefficients of the appropriate molecular orbitals of the potential positions of substitution (16). The attacking radicals are all electron deficient and therefore one would expect that the SOMO's thereof would interact preferentially with the HOMO of 2-benzoylpyrrole. Examination of the squares of the coefficients of both the HOMO and the LUMO of 2-benzoylpyrrole (Table 1) indicates a strong preference for substitution at C-5, as is observed, if the reactions occur through the HOMO.

Experimental

The melting points were determined in a Thomas Hoover "uni melt" capillary melting point apparatus and are not corrected. The infrared spectra were measured with a Nicolet 5 PC FT infrared spectrophotometer. The ^1H nmr spectra were recorded with a Bruker WM 300 or a Bruker AM 500 nmr spectrometer in deuteriochloroform and are expressed as parts per million (δ) from internal tetramethylsilane. The high-resolution mass spectra were obtained with a Finnigan MAT 311A mass spectrometer on samples that were at least 95% pure as judged by nmr spectrometry.

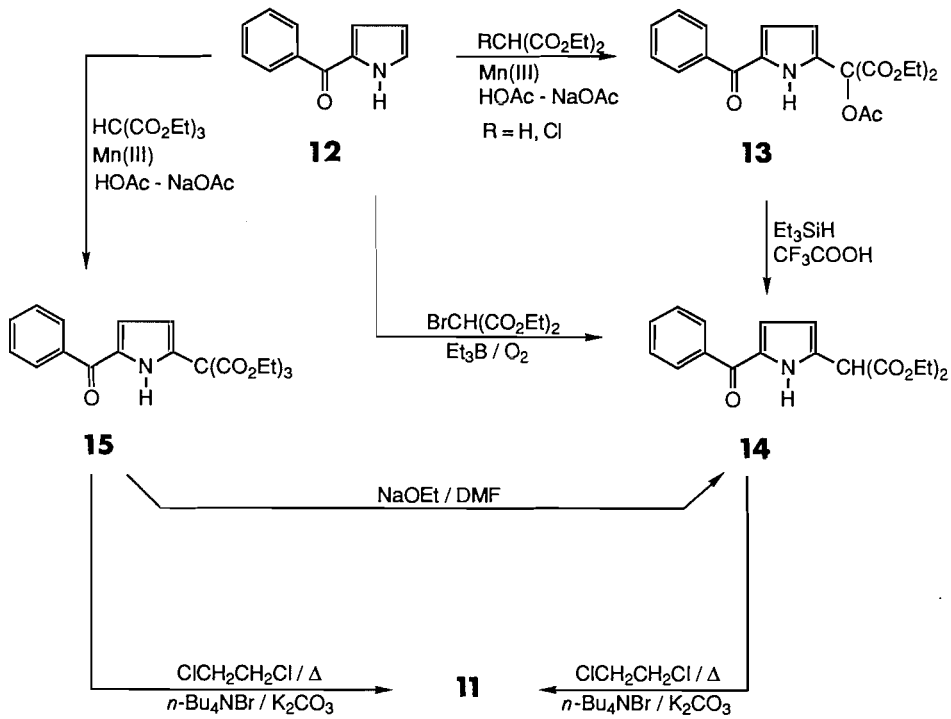
The terms "worked up in the usual manner" or "the usual work-up" signify that the extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*.

1-(2-Iodoethyl)-2-benzoylpyrrole (8)

A solution of the known (6) chloro compound **7** (11.4 g, 49 mmol) in acetonitrile (250 mL) containing sodium iodide (14.7 g, 98 mmol) was heated at reflux temperature for 24 h. The cooled solution was concentrated to a small volume *in vacuo*, water was added to the residue, and the product was extracted into ethyl acetate. After the usual work-up, the residue was subjected to column chromatographic purification on silica gel using hexane – ethyl acetate (97:3) as the eluting solvent. Compound **8**, which because of its solvolytic sensitivity should be used immediately in the next step, was obtained as an oil (12.7 g, 80%); ir (neat): 1623 cm^{-1}; nmr (300) δ: 3.58 (t, 2H, J = 6.84 Hz, CH_2I), 4.71 (t, 2H, J = 6.84 Hz, NCH_2), 6.20 (dd, 1H, $J_{3,4}$ = 4.06 Hz, $J_{4,5}$ = 2.58 Hz, H-4), 6.81 (dd, 1H, $J_{3,4}$ = 4.06 Hz, $J_{3,5}$ = 1.67 Hz, H-3) 7.04 (t, 1H, H-5), 7.43–7.58 (m, 3H), 7.79 (dd, 2H, J_o = 8.27 Hz, J_m = 1.4 Hz); *m/e* calcd. for $C_{13}H_{12}INO$: 324.9962; found: 324.9960.

1-(3,3-Diethoxycarbonylpropyl)-2-benzoylpyrrole (9)

Sodium hydride (60% in mineral oil, 1.35 g, 34 mmol) was added portionwise to a stirred solution of diethyl malonate (5.4 g,



SCHEME 3

TABLE 1. Squares of the coefficients of the pyrrole HOMO's and LUMO's of 2-benzoylpyrrole[a]

Position	HOMO	LUMO
3	0.0920	0.1048
4	0.1483	0.0013
5	0.3347	0.0904

[a]The molecular orbital coefficients are derived from semi-empirical molecular orbital calculations on fully optimized structures. The calculations were carried out using the MNDO Hamiltonian within the implementation of MOPAC 4.0 as released in SYBYL 5.32.

34 mmol) in dry DMF (50 mL) at 0°C. The reaction mixture was then stirred at room temperature for 0.5 h after which time a solution of the iodo compound **8** (11.0 g, 34 mmol) in dry DMF (50 mL) was added. The reaction mixture was stirred at room temperature for 16 h, poured into water, and extracted with ethyl acetate. The extract was washed with water and with saturated NaCl solution, then it was dried (Na_2SO_4) and evaporated *in vacuo*. The residual oil was purified by column chromatography on silica gel using hexane – ethyl acetate (9:1) to elute the malonate ester **9** (9.85 g, 82%) as an oil; ir (neat): 1748, 1732, 1628 cm^{-1}; nmr (500) δ: 1.22 (t, 6H, J = 7.0 Hz, Me), 2.40 (q, 2H, J = 7.2 Hz, CH_2CH), 3.32 (t, 1H, J = 7.3 Hz, CH), 4.15 (q, 4H, J = 7.0 Hz, OCH_2), 4.47 (t, 2H, J = 7.0 Hz, NCH_2), 6.14 (dd, 1H, $J_{3,4}$ = 4.12 Hz, $J_{4,5}$ = 2.58 Hz, H-4), 6.70 (dd, 1H, $J_{3,4}$ = 4.12 Hz, $J_{3,5}$ = 1.76 Hz, H-3), 6.94 (t, 1H, H-5), 7.40 (m, 2H), 7.47 (m, 1H), 7.74 (m, 2H); *m/e* calcd. for $C_{20}H_{23}NO_5$: 357.1576, found: 357.1580.

*1-(3,3-Diethoxycarbonyl-3-bromopropyl)-2-benzoylpyrrole (**10**)*

Sodium hydride (60% in mineral oil, 0.14 g, 3.45 mmol) was added portionwise to a stirred solution of compound **9** (1.12 g, 3.14 mmol) in dry THF (50 mL) at 0°C. The reaction mixture was then agitated at room temperature for 0.5 h after which time *N*-bromosuccinimide (0.64 g, 3.45 mmol) was added. After a further 0.5 h, the reaction mixture was poured into water and the product was extracted into ether. The extract was washed with water and with saturated NaCl solution, and then it was dried and evaporated in *in vacuo*. The residue was subjected to column chromatographic purification on silica gel using hexane – ethyl acetate (9:1) to elute the bromo compound **10** (1.15 g, 84%) as an oil; ir (neat): 1741, 1627 cm^{-1}; nmr (300) δ: 1.29 (t, 6H, J = 7.13 Hz, Me), 2.87 (t, 2H, J = 7.37 Hz, CH_2), 4.26 (m, 4H, OCH_2), 4.61 (d, 2H, J = 7.37; NCH_2), 6.17 (dd, 1H, $J_{3,4}$ = 4.07 Hz, $J_{4,5}$ = 2.55 Hz, H-4), 6.73 (dd, 1H, $J_{3,4}$ = 4.07 Hz, $J_{3,5}$ = 1.68 Hz, H-3), 7.26 (t, 1H, H-5), 7.44–7.56 (m, 3H), 7.77 (dd, 2H, J_o = 8.2 Hz, J_m = 1.4 Hz). Anal. calcd. for $C_{20}H_{22}BrNO_5$: C 55.05; H 5.08, N 3.21; found: C 54.98, H 5.25, N 3.17.

*Diethyl 5-benzoylpyrrol-2-yl-(α-acetoxy)malonate (**13**)*

(a) From 2-benzoylpyrrole and diethyl malonate

A solution of 2-benzoylpyrrole (0.855 g, 5 mmol) and diethyl malonate (0.800 g, 5 mmol) in acetic acid (30 mL) containing manganese triacetate trihydrate (4.56 g, 15 mmol) and sodium acetate (0.820 g, 10 mmol) was stirred at 70°C under a nitrogen atmosphere for 4 h. The reaction mixture was cooled, diluted with ether, and filtered. The filtrate was washed with 10% NaOH solution and saturated NaCl solution, and then it was dried and evaporated *in vacuo*. The residue was subjected to column chromatographic purification on silica gel using hexane – ethyl acetate (7:3) to elute the α-acetoxy compound **13** (1.10 g, 57%) as an oil; ir (neat): 3426, 3263, 1753, 1629 cm^{-1}; nmr (300) δ: 1.30 (t, 6H, J = 7.13 Hz, Me), 2.25 (s, 3H, MeCO), 4.33 (m, 4H, OCH_2), 6.40 (dd, 1H, $J_{3,4}$ = 3.97 Hz, $J_{NH,3}$ = 2.65 Hz, H-3), 6.78 (dd, 1H, $J_{3,4}$ = 3.97 Hz, $J_{NH,4}$ = 2.65 Hz, H-4), 7.47–7.58 (m, 3H), 7.87 (dd, 2H, J_o = 8.30 Hz, J_m = 1.4 Hz), 10.31 (bs, 1H, NH); *m/e* calcd. for $C_{20}H_{21}NO_7$: 387.1318; found: 387.1326.

(b) From 2-benzoylpyrrole and diethyl chloromalonate

The reaction was carried out exactly as in (*a*) and on the same scale but diethyl chloromalonate was used. Compound **13** was obtained in 75% yield.

*Diethyl 5-benzoylpyrrole-2-malonate (**14**)*

*(a) By reduction of acetoxy compound **13***

Trifluoroacetic acid (0.168 g, 1.47 mmol) was added to a solution of the acetoxy compound **13** (0.142 g, 0.367 mmol) in dichloromethane (10 mL) containing triethylsilane (0.102 g, 0.440 mmol) and the solution was then stirred at 40°C for 24 h. Additional triethylsilane (0.102 g) and trifluoroacetic acid (0.168 g) were added and stirring at 40°C was continued for a further 24 h. The cooled solution was washed with cold 10% NaOH solution and then worked up in the usual manner. The residue was subjected to column chromatographic purification on silica gel, the product (0.060 g, 50%) being eluted with hexane – ethyl acetate (87:13) as an oil; ir (neat): 3264, 1739, 1611 cm^{1}; nmr (300) δ: 1.30 (t, 6H, J = 7.23 Hz, Me), 4.26 (m, 4H, OCH_2), 4.81 (s, 1H, CH), 6.29 (d, 1H, $J_{3,4}$ = 3.9 Hz, H-3),[5] 6.80 (d, 1H, $J_{3,4}$ = 3.98 Hz, H-4),[5] 7.45–7.56 (m, 3H), 7.88 (m 2H), 10.19 (bs, 1H, NH). Anal. calcd. for $C_{18}H_{19}NO_5$: C 65.64, H 5.81, N 4.25; found: C 65.61, H 5.80, N 4.25.

(b) From 2-benzoylpyrrole and diethyl bromomalonate

A 1.0 M solution of triethylborane in hexane (2 mL) was added to a stirred solution of 2-benzoylpyrrole (0.171 g, 1.0 mmol) and diethyl bromomalonate (1.185 g, 5.0 mmol) in benzene (20 mL) that was open to the atmosphere. Additional triethylborane solution was added at the end of 1 h (2 mL) and 2 h (1 mL) at room temperature. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with saturated NaCl solution and then worked up in the usual manner. After purification of the crude product as described above, the pure malonate **14** was obtained as an oil (0.284 g, 86%) identical to that prepared by method (*a*).

*(c) By deethoxycarbonylation of triester **15***

Ethanol (0.176 mL, 0.138 g, 3.0 mmol) was added to a stirred suspension of 50% sodium hydride in mineral oil (0.048 g, 1.0 mmol) in anhydrous DMF (10 mL). After ca. 10 min a solution of **15** (0.403 g, 1 mmol) in dry DMF (5 mL) was added and stirring was continued for 2 h at room temperature. The reaction mixture was poured into aqueous ammonium chloride solution and the product was extracted into ethyl acetate. After the usual work-up the crude malonate ester **14** was purified by column chromatography on silica gel (40 g) using hexane – ethyl acetate (4:1) as the eluting solvent. Pure **14** was obtained as an oil (0.273 g, 83%) identical to material prepared by methods (*a*) or (*b*).

*Diethyl 5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1,1-dicarboxylate (**11**)*

*(a) By Mn(III) induced cyclization of **9***

Potassium permanganate (0.138 g, 0.875 mmol), acetic anhydride (1.25 mL, 1.35 g, 10.5 mmol), and sodium acetate (0.420 g, 5 mmol) were added sequentially to a stirred solution of manganese diacetate tetrahydrate (0.858 g, 3.5 mmol) in acetic acid (8 mL) at 80°C. A solution of the malonate ester **9** (0.500 g, 1.40 mmol) in acetic acid (2 mL) was added thereto and the solution was stirred at 80°C for 6 h. The solution was poured into water and the product was extracted into toluene. After the usual work-up the bicyclic ester **11** was obtained as an oil (0.478 g, 96%), which was pure as judged by nmr spectroscopy; ir (neat): 1738, 1626 cm^{-1}; nmr (500) δ: 1.29 (t, 6H, J = 7.10 Hz, Me), 3.13 (t, 2H, J = 7.0 Hz, CH_2C), 4.26 (q, 4H, J = 7.10 Hz, OCH_2), 4.54 (t, 2H, J = 7.0 Hz, NCH_2), 6.27 (d, 1H, $J_{6,7}$ = 4.07 Hz, H-7), 6.84 (d, 1H, $J_{6,7}$ = 4.07 Hz, H-6), 7.43–7.54 (m, 3H), 7.82 (dd, 2H, J_o = 8.3 Hz, J_m = 1.4 Hz); *m/e* calcd. for $C_{20}H_{21}NO_5$: 355.1420; found: 355.1413.

*(b) From **9** using Mn(II) and sodium persulfate*

A solution of manganese diacetate tetrahydrate (0.343 g, 1.40 mmol), silver nitrate (0.024 g, 0.14 mmol), sodium acetate (0.420 g, 5 mmol), acetic anhydride (0.5 mL, 0.54 g, 4.20 mmol), and sodium persulfate (0.333 g, 1.40 mmol) in acetic acid (8 mL) was stirred at 80°C for 0.5 h. A solution of the malonate ester **9** (0.500 g, 1.4 mmol) in acetic acid (2 mL) and additional sodium persulfate (0.333 g, 1.4 mmol) were added and the solution was stirred at 80°C for 12 h. After work-up of the reaction mixture as described in (*a*) compound **11**, identical to that obtained above, was isolated as an oil (0.475 g, 95%).

*(c) By the triethylborane induced cyclization of bromomalonate **10***

This reaction was carried out exactly as described for the synthesis of compound **14** from 2-benzoylpyrrole and diethyl bromomalonate. The crude product was purified by column chromatography on silica gel using hexane – ethyl acetate (85:15). Compound **11** was isolated in 75% yield.

*(d) From malonate ester **14** and 1,2-dichloroethane*

A mixture of tetra-*n*-butylammonium bromide (0.130 g, 0.40 mmol) and potassium carbonate (2.76 g, 20 mmol) in 1,2-dichloroethane (16 mL) containing compound **14** (0.132 g, 0.40 mmol) was stirred at reflux temperature until the starting material had disappeared (~ 24 h). The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was taken up in ether and after the usual work-up the crude material was purified by column chromatography on silica gel using hexane – ethyl acetate (9:1) as the eluant. The product was isolated in 67% yield.

*(e) From triester **15** and 1,2-dichloroethane*

A reaction performed on a 5 mmol scale exactly as described in (*d*) gave **11** in 80% yield.

*5-Benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (**1**, ketorolac)*

A biphasic mixture of the diester **11** (0.600 g, 1.69 mmol) in ether (20 mL) and 20% aqueous NaOH (10 mL) was vigorously stirred at reflux temperature for 24 h. The aqueous layer was washed with ether, carefully made acidic with concentrated hydrochloric acid, and extracted with ethyl acetate. The extract was heated at 70°C for 4 h and then evaporated *in vacuo* to give **1** (0.400 g, 93%) as a solid identical in all respects to an authentic specimen of ketorolac.

[5]After exchange with D_2O.

Acknowledgement

We thank Saul Jaime for converting the triester **15** to the malonate ester **14** and for preparing an analytical specimen of the latter compound.

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