New Protocols for the Synthesis of Substituted 4-*O*-Methyl Tetramates

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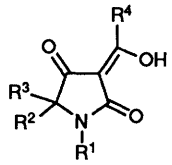
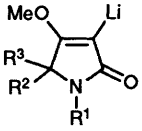
The deprotonation behaviour of 4-methoxypyrrol-2(5*H*)-ones (4-*O*-methyl tetramates) is defined and exploited to provide methods for the synthesis of methyl tetramates variously substituted at N-1, C-5, and C-3.

The pyrrolidine-2,4-dione (tetramic acid) and 4-methoxypyrrol-2(5*H*)-one (4-*O*-methyl tetramate) units are found in a number of natural products, *e.g.*, 3-acyltetramic acids (**1**).[1] A previous communication from these laboratories reported the kinetic deprotonation of a methyl tetramate (**2a**) carrying a single C-5

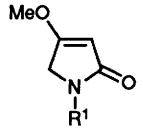


(**1**) **a**; $R^1 = R^2 = Me$, $R^3 = CH_2Ph$, $R^4 = (CH_2)_2Me$

(**2**) **a**; $R^1 = Me$, $R^2 = CHMe_2$
b; $R^1 = Me$, $R^2 = CH_2Ph$
c; $R^1 = R^2 = CH_2Me$



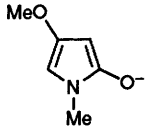
(**3**) **a**; $R^1 = Me$, $R^2 = CHMe_2$, $R^3 = H$



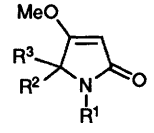
(**4**) **a**; R = Me
b; R = H
c; R = $SiMe_2Bu^t$
d; R = CH_2Ph
e; R = CH_2Me

substituent to form the vinyl-lithium (**3a**);[2] reaction of the vinyl-lithium with aldehydes is the basis of an acylation sequence at C-3. In contrast, an investigation of synthetic routes to methyl tetramates (**2**) found that deprotonation of the 5-unsubstituted derivative (**4a**), under the same conditions, occurred instead at C-5 to afford the dienolate (**5**).[3] To develop the utility of organolithiums (**3**) a proper definition of the base-promoted chemistry of methyl tetramates is needed. We report the results of such a study which provide a portfolio of methods for the production of methyl tetramates variously substituted at N-1, C-5, and C-3.

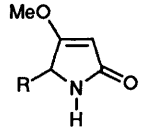
The particular effectiveness of the 5-isopropyl substituent in promoting C-3 deprotonation was first signalled during attempts to prepare the 5-benzyl-1-methylpyrrol-2(5*H*)-one (**2b**), required for other investigations. Treatment of (**4a**) with butyl-lithium (1.2 mol equiv., THF, −78 °C) and benzyl bromide (0.5–1.0 mol equiv.)[3] under a variety of addition regimes afforded (**2b**) but with the 5,5-dibenzyl-1-methyl derivative (**6a**) as the major product [ratios 1:2.7–1:4; typically 12% (**2b**): 38% (**6a**)].† Proton exchange must be occurring between the dienolate (**5**) and the 5-benzyl derivative (**2b**), indicating that the 5-unsubstituted (**4a**) and 5-monosubstituted (**2b**) have comparable acidities and that the latter is also deprotonated at C-5 under these conditions. No evidence of



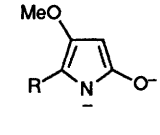
(**5**)



(**6**) **a**; $R^1 = Me$, $R^2 = R^3 = CH_2Ph$
b; $R^1 = R^2 = R^3 = CH_2Ph$
c; $R^1 = R^2 = R^3 = CH_2Me$
d; $R^1 = R^2 = CH_2Me$, $R^3 = CH_2Ph$
e; $R^1 = R^2 = Me$, $R^3 = CH_2Ph$



(**7**) **a**; R = CH_2Ph
b; R = Me
c; R = CH_2Me



(**8**) **a**; R = H
b; R = CH_2Ph

deprotonation at C-3 was obtained. We reasoned that the vinyl-lithium formation from (**2a**) was controlled by steric factors, that dienolate formation was the more usual pathway under both kinetic and thermodynamic conditions, and that to exploit lithiation at C-3 would generally require a 1,5,5-trisubstituted substrate.[4] These conclusions were substantiated by the following results of experiments designed to access a variety of substituted pyrrol-2(5*H*)-ones.

Monobenzylation at C-5 of the NH-tetramate (**4b**) *via* (**4c**)[3] afforded (**7a**) ($LiNPr^i_2$, $PhCH_2Br$, THF, −78 °C; then aq. HF; 63%). A more direct approach to C-5 monoalkylation, however, is the treatment of (**4b**) with an excess of base ($LiNPr^i_2$, 3 mol equiv., THF, −78 °C) and *C*-alkylation of the dianion (**8a**). In this way, (**7a–c**) were prepared using benzyl bromide, iodomethane, and iodoethane (73, 66, and 63%, respectively). Formation of a related dianion (**8b**) from (**7a**) (BuLi, 2.5 mol equiv., THF, −78 °C) was demonstrated by quenching at C-5 with (*E*)-but-2-enal to afford a separable mixture of the epimeric tetrahydropyrrolizines (**9a,b**),‡ resulting from 1,4-addition, and the 1,2-adduct (**10a**) (37, 18, and 22%, respectively). The unstable adducts were efficiently oxidised (MnO_2, CH_2Cl_2) to give (**9c,d**) and (**10b**) (93, 89, and 86%, respectively).

Phase-transfer (PT) conditions (KOH, Bu_4NHSO_4, THF, 25 °C, 20 h)[5] are known to mediate *N*-alkylation of methyl

† All new compounds gave spectral data (IR, UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

‡ The relative configurations of (**9a,b**) were secured by NOE measurements in their ^1H NMR spectra.

Table. Acylation at C-3 of 1,5,5-trisubstituted 4-*O*-methyl tetramates (**6**).

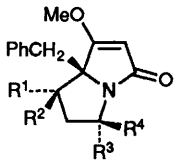
Methyl tetramate (**6**)	3-Hydroxyalkyltetramate (**11**) (yield %)	3-Acyltetramate (**12**) (yield %)
(**6a**)	(**11a**) (73)	(**12a**) (82)
(**6c**)	(**11b**) (88)	(**12b**) (96)
(**6c**)	(**11c**) (70)	(**12c**) (91)
(**6c**)	(**11d**) (85)	(**12d**) (94)
(**6e**)	(**11e**) (73)	(**12e**) (93)
(**6e**)	(**11f**) (79)	(**12f**) (89)
(**6e**)	(**11g**) (71)	(**12g**) (89)

tetramate (**4b**).[3] We found that this method could be extended to *C*-alkylation and multiple alkylations with changed stoicheiometry of the reagents. Thus, whereas the *N*-benzyltetramate (**4d**) was prepared (55%) from (**4b**) using KOH (1.4 mol equiv.) and $PhCH_2Br$ (3 mol equiv.), the tribenzyl compound (**6b**) (67%) was obtained using 10 mol equiv. each of these reagents.* The same conditions with iodoethane produced the *N*-ethyl compound (**4e**) (48%) or the 1,5-diethylpyrrol-2(5*H*)-one (**2c**) (69%), respectively;† further PT treatment of (**2c**) [KOH (3 mol equiv.), RHal (9 mol equiv.)] afforded the triethyl derivative (**6c**) (RHal ≡ EtI; 62%) or the 5-benzyl-1,5-diethyl compound (**6d**) (RHal ≡ $PhCH_2Br$; 71%). The normal sequence of deprotonation of a methyl tetramate is therefore confirmed as N-1, C-5, and C-5 again, with dienolate alkylation occurring at C-5.

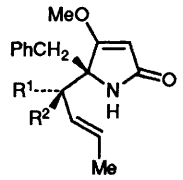
A combination of procedures can be used to assemble 4-methoxypyrrol-2(5*H*)-ones with a variety of alkyl substitution. Thus, an alternative (and more efficient) protocol for conversion of the diethyl compound (**2c**) into 1,5,5-trisubstituted pyrrol-2(5*H*)-ones (**6c**) (83%) and (**6d**) (80%) comprises treatment with BuLi (THF, −78 °C) and iodoethane or benzyl bromide, respectively. Similarly, the 5-benzyltetramate (**7a**), prepared from (**4b**) by the $LiNPr^i_2$ method (see above), was converted *via* the 5-benzyl-1-methyl compound (**2b**) [PT, KOH (1.4 mol equiv.), MeI (3 mol equiv.); 88%] into the 5-benzyl-1,5-dimethylpyrrol-2(5*H*)-one (**6e**) by two methods [PT, KOH (3 mol equiv.), MeI (9 mol equiv.); 67%; or BuLi, MeI, THF, −78 °C; 79%].

The 1,5,5-trisubstituted methyl tetramates were next examined for deprotonation at C-3. As by now expected, the *N*-methyl and *N*-ethyl compounds (**6a**,**c**,**e**) formed vinyl-lithiums (**3**) (BuLi, 1.6 mol equiv., THF, −78 °C) which were quenched efficiently with butanal, (*E*)-pen-2-tenal, and (*E*,*E*)-hexa-2,4-dienal to form 3-(1-hydroxyalkyl) adducts (**11a–g**) as indicated in the Table.[2] These unstable compounds were oxidised directly (MnO_2, CH_2Cl_2) to the 3-acyl-tetramates (**12a–g**) (Table) in good yield. The smooth conversion of (**11e**) to a 3-acyltetramic acid (**1a**) was demonstrated (0.1M aq. NaOH, 20 °C; 93%).[2] A final limitation on vinyl anion formation was observed with the tribenzylpyrrol-2(5*H*)-one (**6b**), where treatment with butyllithium and (*E*)-pent-2-enal as above afforded the tetrahydropyrrolo[1,2-*b*]oxazole adduct (**13**) arising from deprotonation of the *N*-benzyl group.[6]

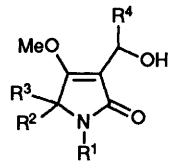
These findings comprise (with our earlier report) a flexible set of methods for the assembly of N-1 and C-5 (poly)alkylated methyl tetramates and define clearly the limits to the vinyl anion strategy for reaction at C-3.



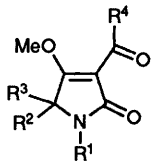
(**9**) **a**; R^1 = Me, R^2 = R^4 = H, R^3 = OH
b; R^1 = R^4 = H, R^2 = Me, R^3 = OH
c; R^1 = Me, R^2 = H, R^3, R^4 = O
d; R^1 = H, R^2 = Me, R^3, R^4 = O



(**10**) **a**; R^1, R^2 = H, OH
b; R^1, R^2 = O

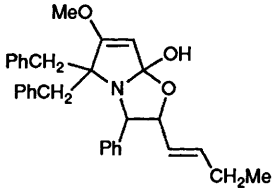


(**11**)



(**12**)

a; R^1 = Me, R^2 = R^3 = CH_2Ph, R^4 = CH═CHCH$_2$Me
b; R^1 = R^2 = R^3 = CH_2Me, R^4 = $(CH_2)_2Me$
c; R^1 = R^2 = R^3 = CH_2Me, R^4 = CH═ CHCH$_2$Me
d; R^1 = R^2 = R^3 = CH_2Me, R^4 = $(CH═CH)_2Me$
e; R^1 = R^2 = Me, R^3 = CH_2Ph, R^4 = $(CH_2)_2Me$
f; R^1 = R^2 = Me, R^3 = CH_2Ph, R^4 = CH═ CHCH$_2$Me
g; R^1 = R^2 = Me, R^3 = CH_2Ph, R^4 = $(CH═CH)_2Me$



(**13**)

Acknowledgements

We thank SERC and Roussel Laboratories for a CASE studentship (J. M. P.).

References

1 For leading references, see: R. C. F. Jones and J. M. Patience, *Tetrahedron Lett.*, 1989, **30**, 3217; J. L. van der Baan, J. W. F. K. Barnick, and F. Bickelhaupt, *Tetrahedron*, 1978, **34**, 223.
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3 R. C. F. Jones and A. D. Bates, *Tetrahedron Lett.*, 1986, **27**, 5285.
4 For a comparison with the behaviour of the oxygen heterocyclic analogues (4-*O*-methyl tetronates), see: A. Pelter, R. I. H. Al-Bayati, M. T. Ayoub, W. Lewis, R. Pardasani, and R. Hansel, *J. Chem. Soc., Perkin Trans. 1*, 1987, 717; N. G. Clemo and G. Pattenden, *ibid.*, 1985, 2407; R. R. Schmidt and R. Hirsenkorn, *Tetrahedron*, 1983, **39**, 2043.
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* Longer reaction times and increased molar quantities of base and alkyl halide caused extensive decomposition.
† Alkylation with iodomethane gave mixtures of di- and tri-methyl products containing some *O*-alkylated materials.

Paper 0/01372B
Received 29*th March* 1990
Accepted 24*th May* 1990