Alkylation of substituted 2,5-dihydropyrrol-2-ones at the 3- and 5-positions

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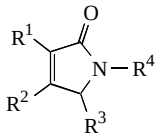
The alkylation and Michael reaction of dihydropyrrol-2-ones have been performed under mild conditions.

Substituted 2,5-dihydropyrrol-2-ones **1** have recently attracted the attention of synthetic chemistry[1–4] due to their high herbicidal activity. Nonetheless, the screening of a sufficient variety of structures requires simple and easily applicable synthetic methods for making libraries by derivatising **1** at the 1-, 3-, 4- and 5-positions (the 2-position being occupied by the oxo group). That is why substitution reactions of **1** are of use in allowing access to a greater range of candidates for structure–activity relationship elucidation. In a number of cases,[5–8] the modification of **1** was performed by lithiation of 3- or 4-substituted **1** by lithium diisopropylamide (LDA) followed by alkylation,[5–7] aldol reaction[6] or Michael addition.[8] The replacement of a single hydrogen at the 5-position in 5-substituted **1** was observed under milder conditions.[6] Nonetheless, the selectivity of substitution at the 3- and 5-positions has not been studied in detail.



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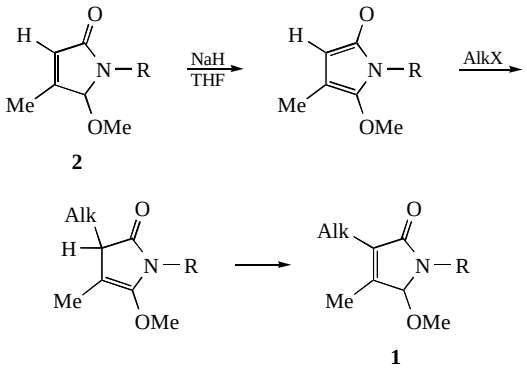
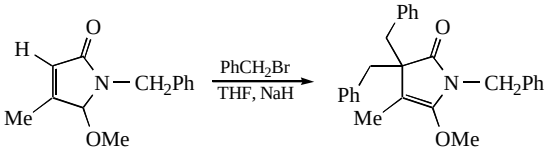
We have found that 1-phenyl- and 1-benzyl-4-methyl-5-methoxy-2,5-dihydropyrrol-2-ones **2** (R = Ph, CH_2Ph) can be alkylated at the 3-position under mild conditions using NaH and alkyl halide in THF (Scheme 1; Table 1, runs 1–4).



Scheme 1

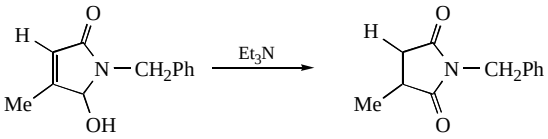
The probable route involves formation of aromatic anion and its subsequent alkylation followed by prototropic rearrangement to give product **1** (Scheme 1).

Note that an alternative alkylation of **2** at the 5-position was not observed. The benzylation of **2** in the presence of an excess of the reagent leads to double substitution at the 3-position, with accompanying migration of the double bond, as well as mono-substitution at this position (Scheme 2; Table 1, run 5).



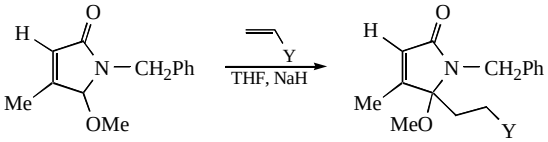
Scheme 2

In separate experiments, we have shown that 1-benzyl-3,4-dimethyl-5-hydroxy-2,5-dihydropyrrol-2-one is a stable tautomer, while 1-benzyl-4-methyl-5-hydroxy-2,5-dihydropyrrol-2-one is easily converted under basic conditions into the isomeric methylsuccinic imide (Scheme 3).



Scheme 3

In contrast to the alkylation, Michael additions of the anion of **2** take place at the 5-position (Scheme 4; Table 1, runs 6 and 7). The reaction with acrylonitrile is complete within 40 h, but for the addition to methyl acrylate at 50 °C, the yield does not exceed 5%.



Scheme 4

The attempted reactions of 1-benzyl-3,4-dimethyl-5-methoxy-2,5-dihydropyrrol-2-one **3** in the presence of sodium hydride or potassium *tert*-butoxide were unsuccessful (Table 2, runs 1–3) while the use of LDA leads to tar formation (Table 2, run 4).

Even the reaction with acrylonitrile, which would be expected to take place at the 5-position, provides none of the desired product. In order to perform the alkylation and Michael addition at the 5-position of 3,4-dialkylpyrrol-2-ones, we prepared 1-benzyl-3,4-dimethyl-5-ethylthio-2,5-dihydropyrrol-2-one **4**, which possesses a lower pK_a due to stabilization of the carbanion.

Indeed, the alkylation of **4** by alkyl halides proceeds in the presence of sodium hydride (Scheme 5; Table 2, runs 5–7) with formation of expected 5-substitution product, but 3-substitution still predominates, accompanied by double bond migration. The introduction of a tertiary N-substituent results in some improvement in the overall yield of the process (Table 2, runs 5 and 12).

The Michael addition reactions of **4** proceeds selectively at the 5-position with good yields (Table 2, runs 8–11). The introduction of a tertiary nitrogen substituent somewhat retards the

Table 1 The alkylation of substituted 4-methyl-5-methoxy-2,5-dihydropyrrol-2-ones (R^1 = H, R^2 = Me, R^3 = OMe) **1** at the 3- and 5-positions by NaH and an alkylating reagent (THF, 20 °C).

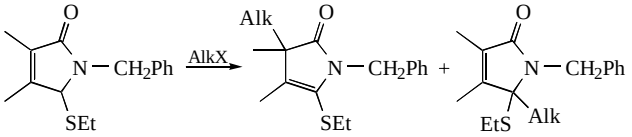
Run	R^4	Equiv. NaH	Reagent (equiv.)	Time/h	Position	Yield[a] (%)
1	Ph	2	MeI (2)	60	3	45
2	$PhCH_2$	2	MeI (2)	16	3	80
3	$PhCH_2$	2	EtI (2)	12	3	75
4	$PhCH_2$	2	$PhCH_2Br$ (1)	16	3	60
5	$PhCH_2$	4	$PhCH_2Br$ (3)	60	3,3	50[b]
6	$PhCH_2$	0.1	CH_2=CHCN (2)	40	5	80
7	$PhCH_2$	0.1	CH_2=$CHCO_2Me$ (2)	40	5	5

[a]The products were isolated by flash chromatography on silica. [b]16% of the monosubstitution product was formed.

Table 2 The alkylation of substituted 3,4-dimethyl-2,5-dihydropyrrol-2-ones **1** at the 3- and 5-positions by NaH and an alkylating reagent (THF, 20 °C).

Run	R^3	R^4	Base (equiv.)	Reagent (equiv.)	Time/h	Position	Yield[a] (%)
1	MeO	$PhCH_2$	NaH (2)	MeI (2)	40	—	—
2	MeO	$PhCH_2$	Bu^tOK (2)	MeI (2)	40	—	—
3	MeO	$PhCH_2$	NaH (0.1)	CH_2=CHCN (2)	60	—	—
4	MeO	$PhCH_2$	LDA (2)	MeI (2)	12	—	—[b]
5	EtS	$PhCH_2$	NaH (2)	EtI (4)	3	3 and 5	45 and 15
6	EtS	$PhCH_2$	NaH (2)	$BrCH_2CH_2Br$ (2)	2	3 and 5	30 and 5
7	EtS	$PhCH_2$	NaH (2)	$Br(CH_2)_4Br$ (2)	6	3 and 5	21 and 6
8	EtS	$PhCH_2$	NaH (0.1)	CH_2=CHCN (2)	15	3 and 5	0 and 90
9	EtS	$PhCH_2$	NaH (0.1)	CH_2=$CHCO_2Me$ (2)	20	3 and 5	0 and 80
10	EtS	$PhCH_2$	NaH (0.1)	HC≡CCO_2Me (2)	40	5	60[c]
11	EtS	$PhCH_2$	NaH (0.1)	MeCH=$CHCO_2Me$ (2)	20	5	92[d]
12	EtS	DDB[e]	NaH (2)	EtI (4)	40	3 and 5	55 and 29
13	EtS	DDB	NaH (2)	MeI (4)	15	3 and 5	40 and 40
14	EtS	DDB	NaH (0.1)	CH_2=CHCN (2)	20	5	66
15	EtS	DDB	NaH (0.1)	CH_2=$CHCO_2Me$ (2)	20	5	42

[a]The products were isolated by flash chromatography on silica. [b]Unknown tar. [c]28% *cis*- and 32% *trans*-. [d]46% *treo*- and 46% *erythro*-. [e]DDB = α,α-dimethyl-3,5-dichlorobenzyl.



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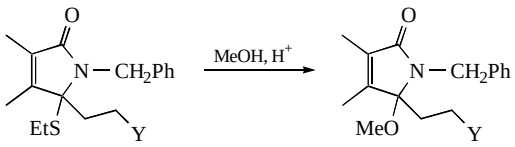
Scheme 5

process. The *cis*- and *trans*-products are formed in almost equal yields in the reaction with methyl propiolate (run 10), and diastereomeric products are obtained with high yields in the reaction with methyl crotonate (run 11).



5 **6**

Scheme 6

The use of activation by sulfur therefore makes it possible to obtain both 5-substituted 3,4-dimethyl-5-ethylthio-2,5-dihydropyrrol-2-ones (Y = COOMe, CN) **5**, and 5-substituted 3,4-dimethyl-5-methoxy-2,5-dihydropyrrol-2-ones **6** (Scheme 6, Table 3) which were obtained in the acid-catalysed methanolysis of **5**.

Table 3 The preparation of 4-methyl-5-methoxy-2,5-dihydropyrrol-2-ones **6** by methanolysis of **5** (2 mmol of **6**, 10 ml of MeOH and 0.2 g of H_2SO_4).

Run	Y	Time/h	Yield (%)
1	CO_2Me	12	68
2	CN	15	52

References

1 B. Boehner and M. Baumann, *Swiss Patent*, 633678, 1982 (*Chem. Abstr.*, 1982, **98**, 121386).
2 T. Kume, T. Goto, M. Honmachida, A. Kamochi, A. Yanagi, S. Yagi and S. Miyachi, *European Patent*, 0286816 A1, 1989 (*Chem. Abstr.*, 1989, **110**, 135246).
3 B. Boehner and M. Baumann, *German Patent*, 2735841 A1, 1978 (*Chem. Abstr.*, 1978, **88**, 152415).
4 G. D. James, S. Mills and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2581.
5 G. B. Gill, G. D. James, K. V. Oates and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2569.
6 R. C. F. Jones and J. M. Patience, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2350.
7 I. Bausanne, A. Chiaroni, H.-P. Husson, C. Riche and J. Royer, *Tetrahedron Lett.*, 1994, **35**, 3931.
8 T. Nagasaka and T. Imai, *Heterocycles*, 1995, **41**, 1927.

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