Tetrahedron Letters Vol. 21, pp 3019 - 3020 0040-4039/80/0801-3019$02.00/0

ALKYLATION OF PROTECTED PIPERAZINONE DIANIONS

John M. Kane* and Albert A. Carr

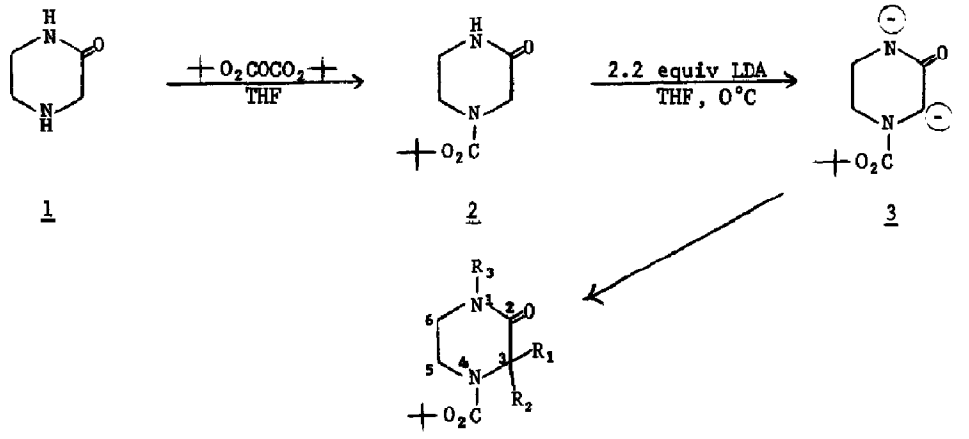
Merrell Research Center
2110 E. Galbraith Road, Cincinnati, Ohio 45215

Summary: A new method for the preparation of substituted piperazinones via alkylation of t-boc-piperazinone is presented.

In conjunction with a program directed toward the syntheses of potential central nervous system agents, we required the preparation of several 3-substituted piperazinones. We now wish to report that alkylation of the dianion of t-boc-piperazinone with various electrophiles offers a synthetically convenient entry into not only 3-monosubstituted piperazinones but also 1,3-disubstituted and 1,3,3-trisubstituted derivatives.

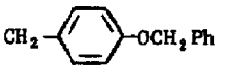
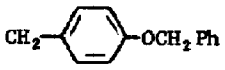
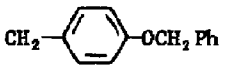
Reaction of the parent heterocycle 1[1] and di-t-butyl dicarbonate[2] readily afforded 2 which was subsequently metalated with 2.2 equivalents of LDA.[3] The resulting dianion 3 was reacted with several alkyl halides giving 3-monosubstituted derivatives 4a-c (Table I). Similarly, employing diphenyl disulfide as an electrophile gave thioether 4d. Sequential reaction of 3 with benzaldehyde and acetyl chloride effected an alkylation/dehydration affording olefin 4e.[4]

SCHEME I



As anticipated, dianion 3 could be 1,3-dialkylated; thus, reaction of 3 with p-benzyloxybenzyl chloride followed by addition of methyl α-bromoacetate gave disubstituted derivative 4f which could also be prepared in stepwise fashion by reaction of 4c with NaH followed by addition of the α-halo ester. In addition, dianions could be regenerated from the monoalkylated products. For example, metalation of 4c with 2.2 equivalents of LDA followed by addition of excess methyl iodide gave trisubstituted derivative 4g.

TABLE I[5]

Compound	R_1	R_2	R_3	Yield[a], %
4a	CH_3	H	H	39
4b	CH_2Ph	H	H	43
4c		H	H	79
4d	SPh	H	H	59
4e	=CHPh		H	40
4f		H	$CH_2CO_2CH_3$	44 (82[b])
4g		CH_3	CH_3	59[c]

(a) Yield for the conversion of 2 to 4; (b) Yield for the conversion of 4c to 4f; (c) Yield for the conversion of 4c to 4g.

We are currently employing the above methodology in the preparations of potential central nervous system agents which will be reported at a later date.

t-Boc-3-(p-benzyloxybenzyl)-piperazinone (4c). To a solution of dry diisopropylamine (7.7 ml, 5.5×10^{-2} mole) in dry THF (25 ml) at 0°C under argon was added dropwise a hexane solution of n-butyllithium (21 ml, 5.5×10^{-2} mole, 2.6 M solution). After ca. 30 min. a solution of 2 (5.0 g, 2.5×10^{-2} mole) in dry THF (125 ml) was added dropwise. After stirring 3 hr at 0° a solution of p-benzyloxybenzyl chloride (6.4 g, 2.7×10^{-2} mole) in dry THF (20 ml) was added via syringe. The reaction was stirred at 0° for an additional hour before the cooling bath was removed and the mixture allowed to warm to room temperature. After stirring overnight the reaction was quenched into sat. aqueous NH_4Cl. The aqueous mixture was extracted with EtOAc (3 times) and the combined extracts were washed with sat. aqueous NaCl before being dried over Na_2SO_4. Filtration of the drying agent and evaporation of the filtrate gave an off-white solid which crystallized from ethyl acetate as colorless prisms: 7.8 g (79%), mp 145-147°C; nmr ($CDCl_3$) 1.31 (s, 9, t-C_4H_9), 2.7-4.3 (m, 6, C_5- and C_6-CH_2, benzylic CH_2), 4.72 (t, 1, C_3-H, J=6.0 Hz), 5.05 (s, 2, OCH_2Ph), 7.02 (q, 4, aromatic), 7.42 (broad s, 6, aromatic, amide NH).

References

1) S. R. Aspinall, J. Amer. Chem. Soc., 62, 1202 (1940).

2) L. Moroden, A. Hallett, E. Wünsch, O. Keller, and G. Wersin, Hoppe-Seylers Z. Physiol. Chem., 357, 1651 (1976).

3) For a review of di- and polyalkali metal derivatives of heterofunctionally substituted organic molecules, see: E. M. Kaiser, J. D. Petty, P. L. A. Knutson, Synthesis, 509 (1977).

4) H. Moureu, P. Chovin, and L. Petit, Bull. Soc. Chim. France, 1785 (1956).

5) All compounds gave satisfactory analytical and spectral data with the exception of 4a, which did not give an acceptable elemental analysis.

(Received in USA 14 April 1980)