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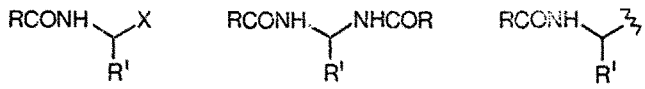
A NEW GENERAL METHOD OF α-AMIDO-ALKYLATION

J. MORTON, A RAHIM AND E.R.H. WALKER*

ICI Pharmaceuticals Division, Alderley Park, Mereside, Macclesfield, Cheshire

Summary : N-(1-p-Toluenesulphonyl-alkyl) amides, which are readily prepared from an aldehyde, an amide and sodium p-toluenesulphinate, are versatile α-amido-alkylating agents for sulphur nitrogen and carbon nucleophiles.

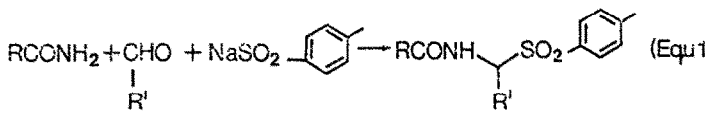
Compounds of type (1, R'=H; X=halogen, -OH, -OR" , -OCOR" , -NHCOR" , $-NR_2$" or $-NR_3$"+) are members of a well known, synthetically important class of α-carboxamido-methylating agents[1].



(1) (2) (3)

Attempted extension of this class of synthon to the preparation of α-carboxamido-alkylating agents (1, R'≠H) fails in all but a few exceptional cases, being restricted almost exclusively to the use of N,N'-alkylidine and N,N'-arylidine-bisamides (2, R'=alk and R'=aryl respectively). We now report the synthesis of a series of sulphones (4), in which the groups R and R' can be aryl, alkyl and substituted alkyl and their use in the α-carboxamido-alkylation of thiols, amines and carbon nucleophiles. The sulphones (4) are therefore electrophilic synthons for the α-carboxamido alkyl moiety (3) and their ready synthesis fills a gap in present synthetic methodology.

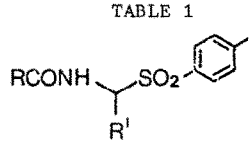
The sulphones (4) are prepared[2] by condensation of an amide, an aldehyde and sodium p-toluene sulphinate in the presence of formic acid, and are stable crystalline solids (eq 1).



(4) (Equ1)

Table 1 lists the sulphones prepared[4]; generally we find that aliphatic amides condense more slowly than benzamide, presumably due to the less nucleophilic amide nitrogen atom.

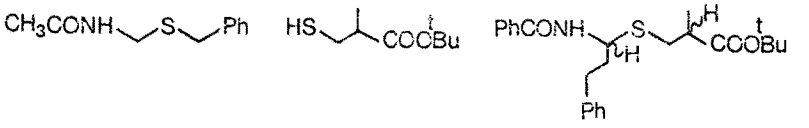
TABLE 1



R =	Ph	Ph	$PhCH_2$	Ph	Ph	CH_3	CH_3
R' =	$PhCH_2$	$PhCH_2CH_2$	$PhCH_2$	CH_3CH_2	Ph	$PhCH_2$	$(CH_3)_2CH$
% Yield	29	60	21	54	40	20	21

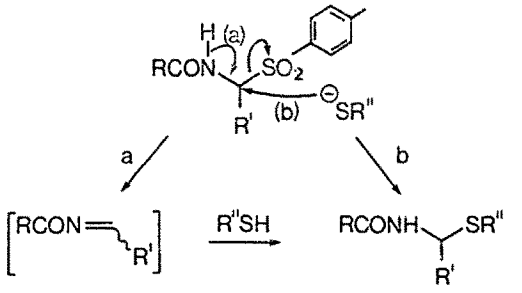
(Yields are not optimised)

These sulphones are versatile α-amido-alkylating agents, reacting readily with sulphur, nitrogen and carbon nucleophiles to give the corresponding α-amido-alkylated products. N-p-Toluenesulphonylmethyl acetamide (4,R=CH_3,R'=H) reacts with benzyl thiol in the presence of potassium t-butoxide to give the thio-ether (5)[5]. In connection with other work we wished to extend this reaction to functionalised thiols. However, under these conditions t-butyl 3-mercapto-isobutyrate (6) failed to react with N(1-p-toluenesulphonyl-3-phenyl-propyl)-benzamide (4,R=Ph,R'=$(CH_2)_2$Ph) to give the expected thio-ether (7) because the potassium salt of the thiol (6) is unstable and decomposes before sulphinate displacement occurs.



(5) (6) (7)

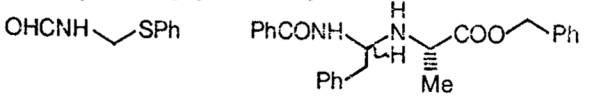
We have investigated the use of alternative bases and find that while triethylamine fails to give significant amounts of the product (7),the use of the more powerful base tetramethylguanidine (pKa 13.4) gives (7)[12] as a mixture of diastereoisomers in 96% yield.
Using the other adducts (Table 1) a range of thio-ethers[13] (9) can be prepared in high yield. Two possible alternative mechanisms to account for the formation of thio-ethers of type (9) are, (a) an elimination of toluene sulphinic acid, to give an acylimine intermediate (8), which is trapped by thiol to give the observed product and, (b) a direct S_N2 sulphinate displacement.



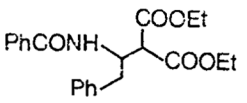
(8) (9)

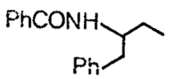
We have not investigated which of these two mechanisms is operating. However, the following observations are relevant. The sulphinate group of N-p-toluenesulphonylmethyl formamide can be displaced by thiophenol in the presence of weak bases such as triethylamine[6] to give thio ether (10). However alkyl thiols, such as benzyl thiol and (6), require strong bases such as potassium t-butoxide or tetramethylguanidine to initiate reaction. Thus the acidity of the thiol governs the base required and this suggests that formation of the thiolate anion is required for reaction to occur. Provided that attack on the acylimine (8) is not rate determining these observations favour mechanism (b) under these conditions, because the base required to initiate mechanism (a) would be independent of the thiol used.
The reaction can be extended to other nucleophiles. Thus primary amines, like S-alanine benzyl ester react with N-(1-p-toluenesulphonyl-2-phenylethyl) benzamide (4, R=Ph,R'=CH_2Ph) in the presence of tetramethylguanidine to give the acyl aminals (11), as an easily separable mixture of diastereoisomers[7] (71% yield) and represents an efficient method of preparing

peptides containing "retropeptide" sequences[8].



(10) (11)





(12) (13)

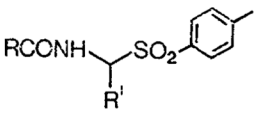
Carbon nucleophiles can also be readily α-amido-alkylated. Reaction of N-(1-p-toluenesulphonyl-2-phenylethyl) benzamide (4,R=Ph, R'=CH_2Ph) with diethylmalonate in the presence of sodium hydride in tetrahydrofuran gives the racemic substituted malonate (12)[9] in 78% yield and treatment with ethyl magnesium bromide (solvent THF) gives[10] the benzamide (13)[11, 4] (51%) Thus the sulphones (4), which are readily prepared from an aldehyde, amide and sodium p-toluene sulphinate, are versatile α-amido-alkylating agents for sulphur, nitrogen and carbon nucleophiles.

A typical sulphone preparation is as follows:- Freshly distilled phenylacetaldehyde (104g), benzamide (96.8g) and sodium p-toluene sulphinate (171.2g) were dissolved in a mixture of water (2l) and formic acid (200ml) in an inert atmosphere of argon. The mixture was refluxed for 2 hours and the yellow crystalline solid isolated by filtration. Recrystallisation from methanol/chloroform gave the product N-(1-p-toluenesulphonyl-2-phenylethyl) benzamide (87g) as a white crystalline solid m.p. 150-2°.

In a typical thioether preparation N-(1-p-toluenesulphonyl-3-phenylpropyl)-benzamide (0.39g) was dissolved in methylene dichloride (5ml) and the thiol (6) (0.2ml) and tetramethylguanidine (0.5ml) added. The reaction mixture was stirred for 2 hours. The product (7) was isolated by pouring the reaction mixture into methylene dichloride (50ml) washing with water, drying over sodium sulphate and evaporating to dryness to give the product (7), which was essentially pure by thin layer chromatography, as an oil (0.39g).

References

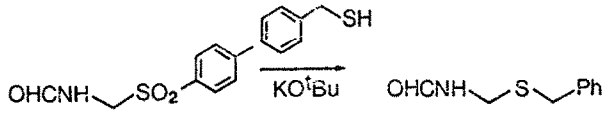
1. H.E. Zaugg and W.B. Martin, Organic Reactions, 1965, 14, 52.
2. The experimental method used is a modification of that used by Olijnsma[3] who reported the preparation of (14).



R=R'=Et
R=R'=Ph

(14)

3. T. Olijnsma, J.B.F.N. Engberts and J. Strating, Recueil, 1967, 86, 463.
4. All new compounds give satisfactory analysis and n.m.r. spectra.
5. We thank Prof.A.M. VanLeusen, Groningen, for communicating the experimental conditions used in the preparation of the formyl derivative (15) prior to publication.



(15)

6. T. Olijnsma, J.B.F.N. Engberts and J. Strating, Recueil, 1972, 91, 209.

7. Diastereoisomer 1, $C_{25}H_{26}N_2O_3$. Theory, C, 74.7; H, 6.5; N, 7.0; Found, C,75.1; H, 6.5;N, 6.5,n.m.r. in deuteriochloroform, 1.2δ, 3H, d, J=9 Hz., $\underline{CH_3}$ CH ; 2.2δ, 1H, s, NH, exchangeable with D_2O; 3.0δ, 2H, d, J=5Hz.,Ph$\underline{CH_2}$CH ; 3.5δ 1H, q, J=9Hz., $CH_3\underline{CH}$; 4.8δ, 2H, q, J=15Hz., Ph$\underline{CH_2}$O; 5.2δ, 1H, m, CONH$\underline{CH}$NH; 6.3δ, 1H, d, J=10Hz., CO$\underline{NH}$; 7.1-7.8δ, 15H, m, aromatic protons. Diastereoisomer 2,n.m.r. in deuteriochloroform 1.25δ, 3H, d, J=9Hz., $\underline{CH_3}$ CH ; 2.2δ, 1H, s, $\underline{NH}$, exchangeable with D_2O; 3.0δ, 2H, m, Ph$\underline{CH_2}$CH ; 3.6δ, 1H q, J=9Hz., $CH_3\underline{CH}$; 5.05δ, 2H, s, Ph$\underline{CH_2}$O; 5.2δ, 1H, m, CONH-$\underline{CH}$-NH; 6.3δ, 1H, d, J=10Hz., CO$\underline{NH}$; 7.1-7.8δ, 15H, m, aromatic protons.

8. M. Chorev, C.G. Wilson and M. Goodman, J.A.C.S., 1977, 99, 8075.

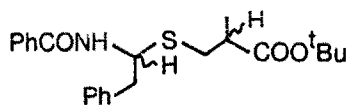
9. $C_{22}H_{25}NO_5$, m.p., 137-8° Theory; C, 68.9; H, 6.5; N, 3.6: Found, C, 68.9; H, 6.5; N, 3.4. n.m.r. in deuteriochloroform; 1.25δ, 6H, quintet (2 overlapping t), $CH_2\underline{CH_3}$; 3.0δ, 2H, d quartet, J_{AB}=14Hz., J_{AX}=10Hz,J_{BX}=8Hz,Ph$\underline{CH_2}$;3.6δ,1H, d, J=4Hz.$(EtOOC)_2\underline{CH}$; 4.2δ,4H,sextet (2 overlapping quartets), $\underline{CH}$2CH3; 5.1δ, 1H, m, PhCH$_3\underline{CH}$; 7.2-7.9δ, 11H, m, aromatic protons and CO$\underline{NH}$.

10. Treatment of 4-phenylsulphonylazetidin-2-one with ethyl magnesium bromide gives 4-ethyl-azetidin-2-one. T.Kobayash, N. Ishida and T Hiraoka, J.C.S. Chem. Comm. 1980, 736.

11. N.m.r. in deuteriochloroform; 0.9δ, 3H, t, $CH_2\underline{CH_3}$; 1.5δ, 2H,sextet, $\underline{CH_2}CH_3$; 2.8δ, 2H, d, J=8Hz., Ph$\underline{CH_2}$; 4.3δ,1H, m, CONH-$\underline{CH}$; 5.9δ, 1H, bd, CO$\underline{NH}$; 7.1-7.8δ, 10H, m, aromatic protons.

12. N.m.r. in deuteriochloroform; 1.2δ, 3H, m, $\underline{CH_3}$CH; 1.4δ, 9H, s, $C(\underline{CH_3})_3$; 2.1δ, 2H, m, -$\underline{CH_2}CH_2$Ph; 2.8δ, 5H, m, -S$\underline{CH_2}$-, Ph$\underline{CH_2}$-, $CH_3\underline{CH}$; 5.5δ, 1H, m, -NH$\underline{CH}$; 6.4δ, 1H, m, -CO$\underline{NH}$-; 7.2-7.8δ, 10H, m, aromatic protons.

13. The use of sulphone (4, R=Ph, R'=CH_2Ph) gives the mixed diastereoisomers (16) which are thiomethylenepeptides[14] of BzPheAlaO^tBu, in which the peptide linkage (-CONH-) has been replaced by a thioether methylene linkage (-S-CH_2-)[15]



(16)

14. In methylenethiopeptides the peptide linkage (-CONH-) is replaced by a methylene thioether linkage (-CH_2S-). J.A. Yankeelov, K-F Fok and D.J. Carothers, J.O.C., 1978, 43, 1623; A.F. Spatola and A.L. Bettag, J.O.C., 1981, 46, 2393.

15. For further work see J. Morton, N Renshaw and E.R.H. Walker in press.

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