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THE USE OF ω-IODOAZIDES AS PRIMARY PROTECTED ELECTROPHILIC REAGENTS. ALKYLATION OF SOME CARBANIONS DERIVED FROM ACTIVE METHYLENE COMPOUNDS AND N,N-DIMETHYLHYDRAZONES.

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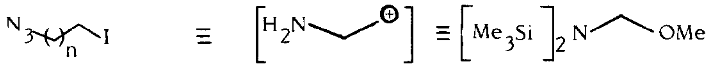
Summary - Some carbanions derived from active methylene compounds and N,N-dimethylhydrazones were alkylated in good yields with the ω-iodoazides **3**, **4** and **13** used as primary amino protected electrophilic reagents.

Primary amino protected electrophilic reagents, i.e. the synthetic equivalents of the synthon **1** with n = 0 are numerous (1). The most interesting reagent for this electrophilic



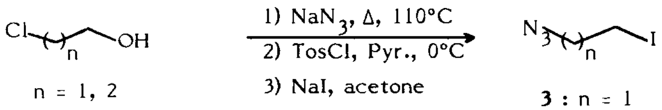
3 : n = 1
4 : n = 2

1

2

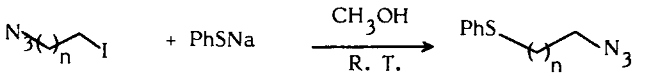
aminomethylation may be the N,N-bis (trimethylsilyl) methoxymethylamine **2** recently proposed by Bestmann (2) and used by others (3). Primary amino protected reagents for electrophilic aminoethylation and propylation i.e. synthetic equivalents of **1** with n = 1 and n = 2 are unknown. In this note, we wish to report on the use of the iodoazides **3** and **4** as alkylating agents. The subsequent chemioselective reduction of the azides thus obtained or their cyclization by an intramolecular aza-Wittig reaction makes them potentially useful reagents for the electrophilic aminoethylation and propylation.

The azides **3** and **4** were easily prepared from chloro-2-ethanol and chloro-3-propanol respectively according to the following scheme :



3 : n = 1
4 : n = 2

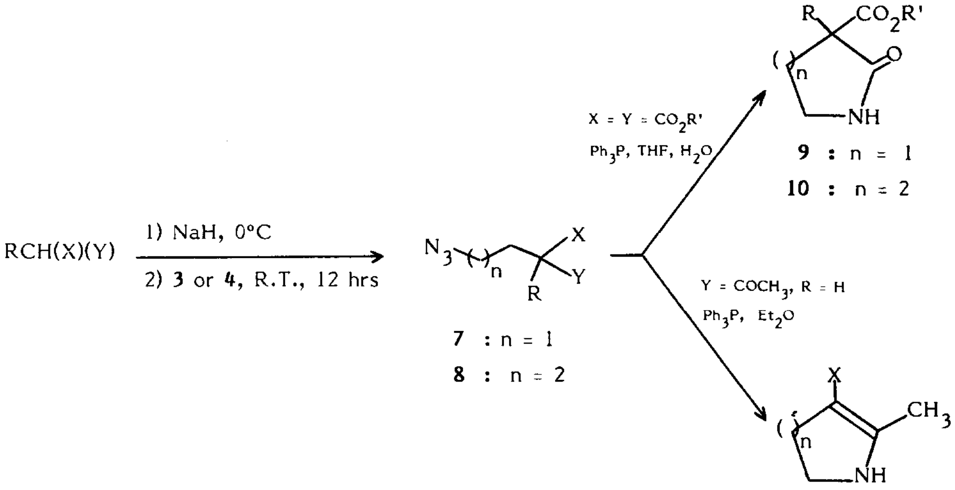
3 and **4** (4) were obtained as slightly yellow oils in overall yields of 65 to 70 % after purification by bulb to bulb distillation (**3** : b.p.$_{20}$ = 70-75°C, **4** : b.p.$_{0,01}$ = 38-40°C) and are storable at 0°C in the dark for several weeks without noticeable decomposition. **3** and **4** readily alkylate sodium thiophenate in methanol leading to the thioazides **5** and **6** which were quantitatively converted to the corresponding primary amines(5).



3 : n = 1
4 : n = 2

5 : n = 1 (89 %; Eb$_{0.01}$=60-62°C)
6 : n = 2 (93 %; Eb$_{0.01}$=68-70°C)

The carbanions generated from active methylene compounds by treatment with NaH in THF or DMF at 0°C were C-alkylated to give the azides **7** or **8** in good to excellent yields (see table).



7 : n = 1
8 : n = 2

9 : n = 1
10 : n = 2

11 : n = 1
12 : n = 2

The chemioselective reduction of the azides **7a, b** and **8a, b** with one equivalent of triphenylphosphine in the presence of a slight excess of water in THF at room temperature (5) led directly to the functionnalized lactams **9** and **10**. The transient primary amines could not be detected. The addition of one equivalent of triphenylphosphine to an etheral solution of **7c**, **8c**, **7d** and **8d** (Y = COMe) resulted in a nitrogen evolution and the formation of the β-enaminoesters **11** and **12** via an intramolecular aza Wittig reaction (6). This constitutes a simple access to that interesting class of heterocycles.

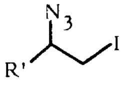
Table (4)

Synthesis of **7**, **8**, **9**, **10**, **11** and **12**

R	X	Y	n	**7** or **8**		**9**, **10**, **11** or **12**	
				% (c)	Eb°C/0.01 torr	% (c,d)	m.p. °C
H	CO_2Me	CO_2Me	1 (a)	**7a** : 78	65-70	**9a** : 90	136-138
H	CO_2Me	CO_2Me	2 (a)	**8a** : 92	80-85	**10a** : 86	110-112
CH_3	CO_2Et	CO_2Et	1 (a)	**7b** : 83	75-80	**9b** : 88	34-36
CH_3	CO_2Et	CO_2Et	2 (a)	**8b** : 94	85-90	**10b** : 90	86-88
H	$\mathrm{Me}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-$	CO_2Et	1 (b)	**7c** : 80 (e)	(f)(g)	**11c** : 88	36-38
H	$\mathrm{Me}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-$	CO_2Et	2 (b)	**8c** : 92 (e)	72-75	**12c** : 90	44-46
H	$\mathrm{Me}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-$	$(\mathrm{EtO})_2\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}-$	1 (b)	**7d** : 68	(f)(h)	**11d** : 72	(f)(j)
H	$\mathrm{Me}\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}-$	$(\mathrm{EtO})_2\overset{\overset{\mathrm{O}}{\|}}{\mathrm{P}}-$	2 (b)	**8d** : 70	(f)(i)	**12d** : 76	(f)(k)

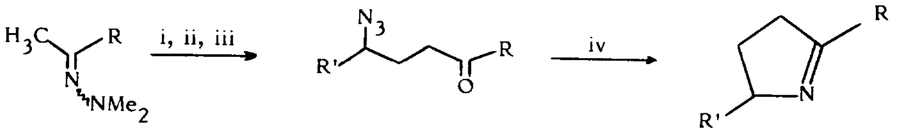
(a) Solvent : THF. (b) Solvent : DMF. (c) Yields are of isolated pure products. (d) From **7** or **8**. (e) Isolated as a 9/1 mixture of keto and enol tautomers. (f) Purified by column chromatography on silica gel. (g) Elution : ether/petroleum ether (1/1 by volume), Rf = 0.52. (h) elution : ether/methanol (95/5), Rf = 0.81. (i) elution : ether/methanol (95/5), Rf = 0.61. (j) elution : ether/methanol (95/5), Rf = 0.31. (k) ether/methanol 95/5, Rf = 0.50.

The carbanions derived from N,N-dimethylhydrazones (7) **14** and **15** were alkylated with the β-iodoazides **3** and **13** (8). After hydrolysis (9), the corresponding ω-azidoketones **16**(4) were obtained with reasonnable yields according to the following scheme.



3 : R' = H

13 : R' = nBu



14 : R = CH$_3$

15 : R = 

16a : R' = H, 56 %
16b : R' = nBu, 54 %
16c : R' = nBu, 41 %

17a : 92 % (Eb$_{760}$:103-105°C)
17b : 84 % (Eb$_{18}$: 86-88°C)
17c : 93 % (Eb$_{18}$: 95-96°C)

i : BuLi, THF, -78°C. ii : **3** or **13**, -78°C → R.T., 18 hrs. iii : ref. (9). iv : Ph$_3$P, ether, R.T., 12 hrs (6).

The addition of one equivalent of triphenylphosphine to the azidoketones **16** in ether at room temperature gave quantitatively the 1-pyrrolines **17** (6) . This sequence constitutes a simple access to this valuable class of heterocycles starting from readily available materials.

Finally, the relative inertness of the azido group towards a number of reagents makes it one of the most versatile potential primary amino function.

References and Notes

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