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MONOALKYLATION OF METHYL CYANOACETATE AND ACETYLACETONE USING 1,8-DIAZA-BICYCLO[5.4.0]UNDECENE-7

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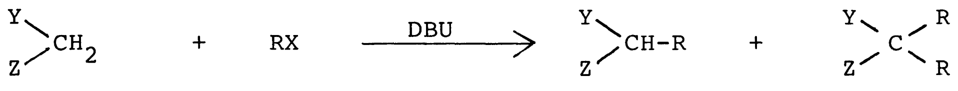
A simple method for selective monoalkylation of methyl cyanoacetate and acetylacetone using 1,8-diaza-bicyclo[5.4.0]undecene-7(DBU) as a base is described.

Alkylation of active methylene compounds is an important reaction in preparative organic chemistry and has been extensively studied.1) A frequently encountered difficulty in such reaction is the concurrent occurrence of mono- and dialkylation. This problem becomes particularly serious in alkylation of methyl cyanoacetate(Ia) or acetylacetone(Ib). We now wish to report a simple method for nearly exclusive monoalkylation of these active methylene compounds using DBU in benzene as a base.

The procedure is quite simple; for example, n-butyl bromide(7.0g, 0.051mol) was added to a solution of Ia(5.0g, 0.05mol) and DBU(7.9g, 0.051mol) in benzene (100ml) and the solution was stirred at room temperature for 15 hours. After filtering off DBU-HBr salt, the solvent was evaporated and the residue was distilled under reduced pressure giving 6.1g(78% yield) of methyl 2-cyanohexanoate (IIa, R = n-C_4H_9), bp. 125°/20mmHg. The crude product was also quantitatively analyzed by VPC using a column containing Silicone-DC-552(20%). The yields of mono- and dialkylated products determined by VPC are given in Table 1. Alkylation of Ia or Ib with various alkyl halides under these conditions took place as readily as described above giving rise to the corresponding monoalkylated product(II) in good yields as shown in Table 1. Triethylamine failed to induce alkylation under similar conditions.



I II III

a: Y = CN, Z = CO_2CH_3

b: Y, Z = $\underset{\overset{\|}{O}}{C}CH_3$

Obviously the use of a non-polar solvent such as benzene is important for this selective monoalkylation, since the ratio of mono- to dialkylation decreased when the reaction was carried out in a polar solvent such as acetonitrile. Alkylation of Ia or Ib with ethyl iodide by the classical method (CH_3ONa in CH_3OH and NaH in DMF) resulted in the formation of considerable amounts of dialkylated product(III) as shown in Table 2. As can be seen from Table 1 and Table 2, the present alkylation method is much simpler and more selective than the classica method and far more superior in these regards to the ion pair extractive method of Brändström2,3)which has been the best selective monoalkylation method known to date.4) Other active methylene compounds such as ethyl acetoacetate or diethyl malonate could be selectively monoalkylated by the present method. The overall results will be published in the full paper.

Table 1 Alkylation of I in benzene in the presence of DBU

Substrate	RX	Time(hr)*	Yield(%)	
			II	III
Ia	C_2H_5I	0.5	83	8
Ia	C_2H_5Br	3	80	7
Ia	$n\text{-}C_3H_7I$	1.5	76	7
Ia	$i\text{-}C_3H_7I$	4	61	1
Ia	$n\text{-}C_4H_9Br$	15	88	4
Ib**	C_2H_5I	2	81	5
Ib**	$n\text{-}C_3H_7I$	4.5	82	4
Ib**	$n\text{-}C_4H_9I$	6.5	80	1

* All reactions were carried out at room temperature.

** The O-alkylated products were also formed in about 3-10% yields.

Table 2 Effect of base and solvent on alkylation with ethyl iodide

Substrate	Base	Solvent	Time(hr)	II(%)	III(%)	II/III
Ia	DBU	Benzene	0.5	83	8	10.4
	DBU	CH_3CN	0.5	65	13	5.0
	NaH	DMF	0.5	51	33	1.6
	CH_3ONa	CH_3OH	0.5	42	37	1.1
	$n\text{-}Bu_4N^+OH^-$*	$CHCl_3$	0.33	72	14	5.1
Ib	DBU	Benzene	2	81	5	16.2
	NaH	DMF	2	72	21	3.5
	CH_3ONa	CH_3OH	14	68	19	3.5
	$n\text{-}Bu_4N^+OH^-$**	$CHCl_3$	0.4	72	16	4.5

All reaction were carried out with the molar ratio of I : base : RX(1 : 1 : 2) at room temperature. *Ref. 2. **Ref. 3.

References

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