Use of the Nonionic Superbase $P(MeNCH_2CH_2)_3N$ in the Selective Monoalkylation of Active-Methylene Compounds

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Received December 31, 1997

The symmetric active-methylene compounds $CH_2(CO_2Et)_2$ and $CH_2[C(O)Me]_2$ are selectively monoalkylated in the presence of 1.1 equiv of a variety of alkyl halides and 1 equiv of the nonionic superbase $P(MeNCH_2CH_2)_3N$ in 85−98% yields in 30 min at room temperature. The unsymmetrical active-methylene compound $EtO_2CCH_2C(O)Me$ is selectively monoalkylated under the same conditions, except for the temperature, which is 0 °C, in 59−88% yields. The observation of selective C- rather than O-alkylation is rationalized in terms of the formation of an enolate whose negatively charged oxygen is sterically protected by a nearby $HP(MeNCH_2CH_2)_3N^+$ counterion in a tight ion pair.

Introduction

Alkylations and acylations of active-methylene compounds, such as malonic esters, β-diketones, and β-keto esters, are important transformations in organic chemistry that have been explored extensively.[1] Monoalkylated products of such substrates are highly useful because of their ready conversion to the corresponding ketenes or esters, and they also function as starting materials for the preparation of α,β-unsaturated ketones[2] and esters.[3]

A frequent difficulty encountered in attempts to monoalkylate the aforementioned substrates is concurrent formation of a second C-alkylated side product, O-alkylated systems and, in some cases, condensation products. Significant O-alkylation is especially favored when the equilibrium concentration of the enol tautomer is relatively high, as with β-keto esters and β-diketones. Numerous attempts to improve the efficiency of C-alkylation have met with limited success. It has been observed that O-alkylation can be inhibited by suppressing the concentration of enolate ion using carefully controlled reaction conditions,[1a] by coordinating the enolate oxygen to a metal cation,[1a] or by employing a hydrogen-bonding solvent.[4] A particularly efficacious procedure for favoring C-alkylation with short-chain alkyl iodides employs crystalline Tl(I) enolates that apparently maintain ion pairing via partially covalent $Tl^+-{}^-O$ binding in solution.[5] However, such salts are not very reactive as nucleophiles, and their reactions require several hours in a refluxing solvent. Although active-methylene compounds can be monoalkylated using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base, yields are moderate, reaction times are relatively long, and dialkylation as well as O-alkylation are observed.[6]

Results and Discussion

Here, we report monoalkylation reactions of **1**−**3** in the presence of the commercially available nonionic superbase **4**. Substrates **1** and **2** are converted to their monoalkylated products **5a**−**g** and **6a**−**g**, respectively (Scheme 1) in very high yields (Table 1) with 100% conversion of starting material and no formation of corresponding dialkylated product (**8a**−**g** and **9a**−**g**, respectively) according to ^{1}H NMR spectroscopy.[7] Although in the case of **3** unreacted starting material as well as dialkylated side products **10a**−**g** were detectable by ^{1}H NMR spectroscopy, respectable yields of monoalkylated product **7a**−**g** were obtained (Table 1) under the mild conditions employed in these reactions (Scheme 1).[7]

We suggest that the ease of alkylation of **1**−**3** encountered with **4** as a base is attributable to a basicity of **4** that exceeds that of DBU by 17 orders of magnitude,[8] thus providing relatively high concentrations of enolate ion for electrophilic attack by RX. We speculate that the selective C-alkylation over O-alkylation we observe is due

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(2) Ono, N.; Tamura, R.; Hayami, J.; Kaji, A. *Chem. Lett.* **1977**, 189.

(3) Ono, N.; Tamura, R.; Hayami, J.; Kaji, A. *Tetrahedron Lett.* **1978**, 763.

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(5) Taylor, E. C.; Hawkes, G. H.; McKillop, A. *J. Am. Chem. Soc.* **1968**, *90*, 2421.

(6) Ono, N.; Yoshimura, T.; Saito, T.; Tamura, R.; Tanikaga, R.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1716.

(7) All reagents were used as received from chemical suppliers. Base **4** was prepared as reported previously (Tang, J.-S.; Verkade, J. G. *Tetrahedron Lett.* **1993**, *34*, 2903). Alkylations of **1** and **2** were carried out under N_2 at 25 °C. Acetonitrile was dried by refluxing over CaH_2, and then it was distilled from CaH_2 under nitrogen. The general procedure for alkylating **1** and **2** was to dissolve 1 mmol each of **4** and active methylene compound in 10 mL of dry CH_3CN with stirring. After the mixture was stirred for 10 min, a solution of 1.1 mmol of alkyl halide in 5 mL of CH_3CN was added under nitrogen and stirring was continued for 30 min. After all volatiles were removed under vacuum, 20 mL of hexanes was added to the residue and the solids were filtered off. The filtered material was subjected once more to the same extraction/filtration cycle. Both filtrates were combined, and the solvent was evaporated to give the alkylated product in >98% purity as determined by ^{1}H NMR spectroscopy. The general procedure for alkylating **3** was to dissolve 1 mmol each of **4** and active methylene compound in 10 mL of dry CH_3CN with stirring. After the mixture was stirred for 30 min at 0 °C, 1.1 mmol of alkyl halide was added under nitrogen, and stirring was continued for 5 min at 0 °C. After all volatiles were removed under vacuum, 20 mL of hexanes was added, and then the solids were filtered off. The filtered material was subjected once more to the same extraction/filtration cycle. Both filtrates were combined, and the solvent was evaporated to give the crude alkylated product. The monoalkylated product was isolated by silica gel column chromatography using gradient elution with hexanes/Et_2O.

S0022-3263(97)02350-5 CCC: $15.00
Published on Web 05/12/1998

Scheme 1

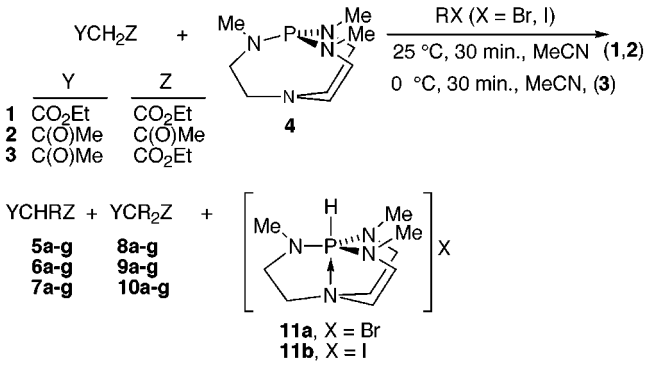
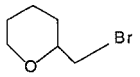
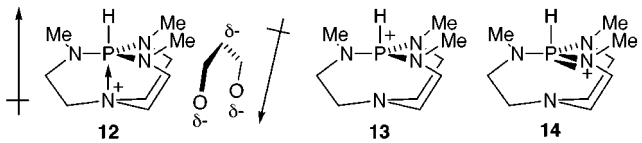


Table 1. Alkylation of 1−3 with RX[a]

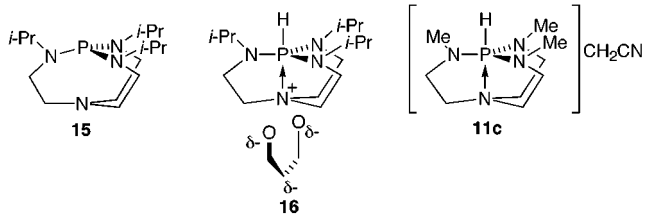
RX	% yield of $CHR(CO_2Et)_2$ from **1**	% yield of $CHR[C(O)Me]_2$ from **2**	% yield of $Me(O)CHRCO_2Et$ from **3**
MeI	98, **5a**[b]	96, **6a**[c]	71, **7a**[j]
EtI	92, **5b**[d]	85, **6b**[c]	78, **7b**[k]
i-PrI	98, **5c**[e]	86, **6c**[c]	70, **7c**[c]
	94, **5d**[f]	94, **6d**[g]	80, **7d**[f]
PhCHBrMe	92, **5e**[e]	98, **6e**[h]	87, **7e**[l]
$MeCHBrCO_2Et$	93, **5f**[i]	95, **6f**	88, **7f**
	88, **5g**	86, **6g**	59, **7g**

[a] Identification of the indicated compounds was made by comparing their ^1H NMR data with those in the references indicated. The ^{13}C and ^1H NMR spectra for the remaining compounds are given in the Supporting Information. [b] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1** (1), 937B, Aldrich Chemical Co., Milwaukee, 1993. [c] Hooz, J.; Smith, J. *J. Org. Chem.* **1972**, *37*, 4200. [d] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1** (1), 938B, Aldrich Chemical Co. Milwaukee, 1993. [e] Cahiez, G.; Alami, M. *Tetrahederon* **1989**, *45*, 4163. [f] Hwu, J.; Chen, C. N.; Shiao, S. S. *J. Org. Chem.* **1995**, *60*, 856. [g] King, J. F.; Rathore, R.; Lam, J. Y.; Guo, Z. R.; Klassen, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 3028. [h] Vallribera, A.; Marquet, J.; Moreno-Manas, M.; Cayon, E. *Tetrahederon* **1993**, *49*, 6437. [i] Ibuka, T.; Aoyagi, T.; Yamaotto, Y. *Chem. Pharm. Bull.* **1986**, *34*, 2417. [j] Padwa, A.; Kulkami, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144. [k] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1** (1), 1096C. [l] Cookson, R. C.; Sadler, D. E.; Salisbury, K. *J. Chem. Soc., Perkins Trans. 2* **1981**, 774.

to steric protection and charge neutralization of the negatively charged enolate oxygens by the large diffusely charged cation of ion pair **12**. Such an ion pair is likely



to be relatively poorly solvated (perhaps even by a solute as polar as CH_3CN) owing to the low charge density in such a sizable species. The suggested average configuration shown for this species may be stabilized by the tendency for head-to-tail alignment of the upwardly directed dipole moment of the cation with the dipole of the anion. (In **12**, the anion is shown without substituents for clarity.) Since most of the cationic charge resides at the axial nitrogen, the enolate oxygens are more charge-neutralized (rendering them less vulnerable to electrophilic attack by RX) than the central carbanionic site of the enolate, which is relatively poorly charge-neutralized by the more diffusely distributed partial positive charge indicated in resonance structure **13** and the three resonance structures implied in **14**. The domination of monoalkylation under our conditions can then be rationalized by assuming that ion pairs such as **12** possess greater reactivities compared with more solvated enolates and that once monoalkylation has occurred, the augmented steric hindrance of that product inhibits the ion−dipole interaction required to establish a monoalkylated form of **12** for promotion of a second alkylation. The increase in dialkylated product and unreacted starting material recorded in the alkylations of **3** may be a consequence of a weaker and/or less well-defined corresponding complex **12**, owing to the lower symmetry of the anion in this case, and hence the decreased symmetry of its negative charge distribution and of its molecular moment. Our rationale for these results is consistent with our observation that by substituting the more sterically hindered and somewhat stronger base **15**[9] for **4** in the reaction of MeI with **2**, the former base led to an increased dialkylation/monoalkylation ratio (7.5:92.5) than for the latter (2:98). The greater bulk of **15** is expected to reduce the interaction of the equatorial region of the trigonal pyramid of the corresponding conjugate acid, thereby leading to a species resembling **16** in which both faces of the enolate can be sequentially alkylated.



Because **4** slowly establishes an equilibrium in acetonitrile consisting of a small but detectable amount of **11c**, it was of interest to determine whether deprotonation of active-methylene substrates of the type employed here occurred by direct attack of the base, as is the case in some dehydrohalogenation reactions, or via the CH_2CN^- anion, as is the case in other dehydrohalogenations we have carried out.[10] When diethyl malonate is reacted at room temperature for 30 min with 1 equiv of **4** in CD_3CN in an NMR tube, the ^{31}P NMR spectrum reveals a singlet at −10.07 ppm corresponding to protonated **4** (i.e., the cation of **11a**−**c**) and a very small 1:1:1 triplet at −10.10 ppm assigned to the *deuterated* analogue of this cation. No peak at 128 ppm corresponding to **4** is observed. Repeating this procedure and then adding 1 equiv of MeI also resulted in the formation of protonated **4**, as expected if **4** deprotonates the more acidic malonate central methylene group preferentially to CD_3CN.

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Acknowledgment. We thank the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Iowa State University Center for Advanced Technology Development for grant support of this research.

Supporting Information Available: ^{1}H and ^{13}C NMR spectral data (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO972350I