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A NEW SYNTHETIC METHOD OF α,β-UNSATURATED KETONES VIA REGIOSELECTIVE REACTION OF ALLYL ANION FORMED FROM 2-MORPHOLINO-3-BUTENENITRILES (MASKED ACYL ANION EQUIVALENTS) WITH ALKYL HALIDES FOLLOWED BY HYDROLYSIS

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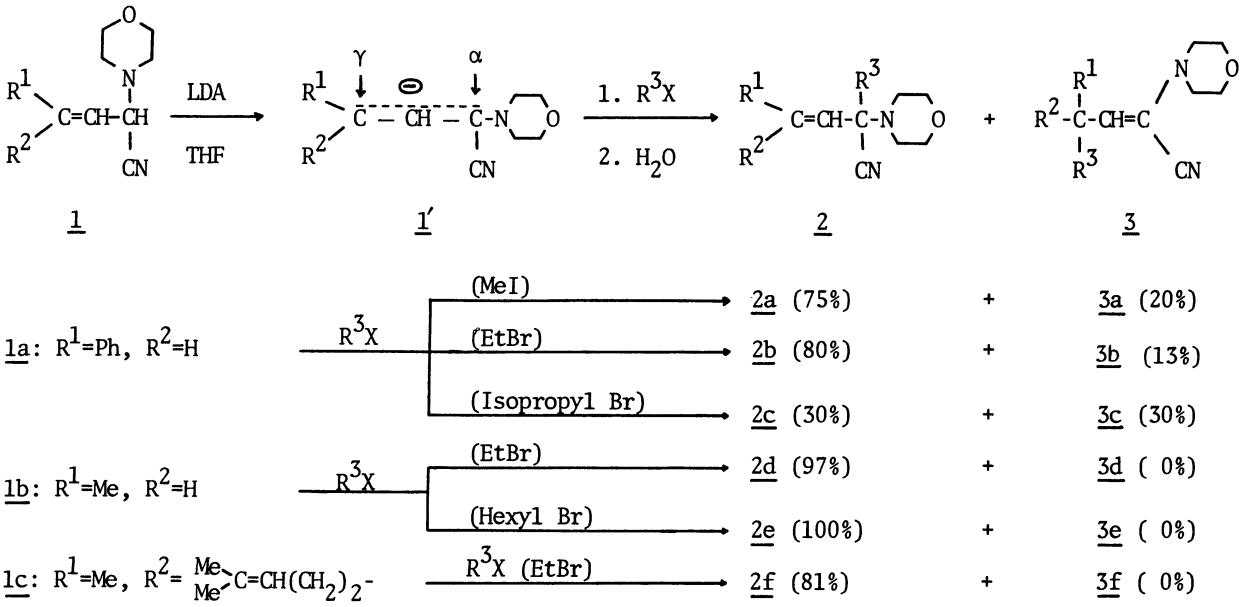
Treatment of 2-morpholino-3-butenenitriles and alkyl halides regioselectively afforded products alkylated on α-position to the nitrile group. The hydrolysis of the α-alkylation products gave the α,β-unsaturated ketones in good yields.

Reaction of allyl anion formed from 2-amino-3-butenenitriles with alkyl halides reportedly gives products (3) preferentially alkylated on γ-position to the nitrile group, when the amino group is N-methylanilino and N-methyl-N-cyclohexylamino.[1] However, the treatment of 2-morpholino-3-butenenitriles (1)[2] with alkyl halides predominantly gave products (2) alkylated on α-position to the nitrile group of 1. The hydrolysis of the α-alkylation products (2) gave the corresponding α,β-unsaturated ketones (4) in good yields. We thus report here a new synthetic method of α,β-unsaturated ketones via regioselective α-alkylation of allyl anion formed from 2-morpholino-3-butenenitriles (1).

The typical alkylation was carried out as follows: Under a dry nitrogen atmosphere, lithium di-isopropylamide (LDA) (2 mmol) dissolved in 2 ml of tetrahydrofuran (THF) was added at -78 °C to a mixture of THF (2 ml) and 2-morpholino-4-phenyl-3-butenenitrile (1a) (2 mmol). After the mixture was stirred for 20-30 min, ethyl bromide (2 mmol) was added dropwise. The dry-ice/acetone bath was then removed and the reaction mixture was stirred for 3 hrs at room temperature. The reaction solution was poured into ice/water, and the aqueous layer was extracted with diethyl ether. Thus, 2-ethyl-2-morpholino-4-phenyl-3-butenenitrile (2b), alkylated on α-position, and 2-morpholino-4-phenyl-2-hexenenitrile (3b), alkylated on γ-position, were obtained in 80% and 13% yields, respectively, as depicted in Scheme 1. Likewise, the treatment of 1a and methyl iodide gave 2-methyl-2-morpholino-4-phenyl-3-butenenitrile (2a) and 2-morpholino-4-phenyl-2-pentenenitrile (3a) in 75% and 20% yields, respectively. The treatment of 1a and isopropyl bromide, however, gave 2-(isopropyl)-2-morpholino-4-phenyl-3-butenenitrile (2c) and 2-morpholino-5-methyl-4-phenyl-2-hexenenitrile (3c) in 30% and 30% yields, respectively, together with a substantial amount of unreacted 1a. The steric hindrance of a bulky isopropyl group appears to be responsible for the lack of regioselectivity and the decreased reactivity. Interestingly, the reaction of 2-morpholino-3-pentenenitrile (1b) with ethyl and hexyl bromides and that of 4,8-dimethyl-2-morpholino-3,7-nonadienenitrile (1c) with ethyl bromide regioselectively afforded only α-alkylation products, i.e. 2-ethyl- and 2-hexyl-2-morpholino-3-pentenenitriles (2d and 2e) in 97% and 100% yields, respectively, and 4,8-dimethyl-2-ethyl-2-morpholino-3,7-nonadienenitrile (2f) in 81% yield, giving no γ-alkylation products (3d, 3e and 3f). The structures of α- and γ-alkylation products (2 and 3) were confirmed by IR, mass and NMR spectroscopy.[3]

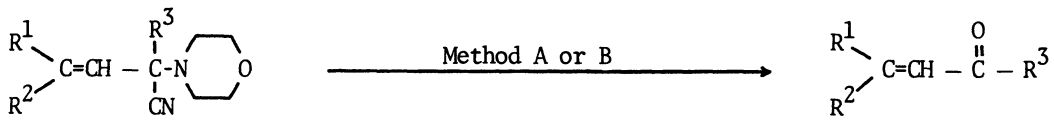
Scheme 1



Hydrolysis of the α-alkylated morpholinonitriles (2) proceeded smoothly under mild conditions (Methods A and B) as shown in Scheme 2. Method A: α-Alkylated morpholinonitrile (2) (1 mmol) was hydrolyzed within several minutes when heated to reflux in 95% ethanol (5 ml) with slightly less than equimolar amount (0.8 mmol) of $CuSO_4.5H_2O$ or preferably with more soluble $Cu(OAc)_2$. After the inorganic salt is filtered off, the α,β-unsaturated ketone was extracted with diethyl ether. The ether layer was washed and dried with anhydrous sodium sulfate. After the ether was removed, the crude product was purified by silica gel-column chromatography. Hydrolysis by Method A is presumed to proceed as follows: Cupric ion removes the cyanide group from the α-alkylated morpholinonitrile (2), precipitating as insoluble $[Cu(CN)_4]^{3-}$ salts.[4] Method B: Hydrolysis of the α-alkylated morpholinonitrile (2) could also be done simply on a silica gel column. When the α-alkylated morpholinonitrile (2a or 2f) was adsorbed on to the silica gel column (40 x weight of 2) through which the mixed solvent of benzene and hexane (85:15 V/V) as an eluting solution was passed, the corresponding α,β-unsaturated ketone (4a or 4f) was eluted in a high yield. This silica gel procedure transformed the α-alkylated morpholinonitrile (2) directly into the corresponding ketones. This procedure is known to be useful to liberate carbonyl compounds having acid-sensitive groups. For example, an acetal function is retained by the silica gel procedure.[5] The hydrolysis of 2d and 2e regioselectively obtained in high yields did not give favorable results. For example, attempted hydrolysis of 2d by either Method A or B gave unknown polimerized products, not the corresponding α,β-unsaturated ketone (4d). Hydrolysis of 2e by Method A, on the other hand, gave 2-decene-4-one (4e) in 40% yield together with a substantial amount of polimerized products. The structure itself of 2d and 2e having a framework of crotonaldehyde may be unstable even under mild conditions of the hydrolysis and responsible for the formation of the polimerized products. The structures of α,β-unsaturated ketones were confirmed by IR, mass and NMR spectroscopy.[6]

The regioselective α-alkylation has advantages of simplicity of the reaction procedure for preparation of α,β-unsaturated ketones, and ready availability of α-aminoacetonitriles related as masked acyl anion equivalents. Work is in progress to extend the synthetic scope for formation of C-C bond using α-aminoacetonitriles.

Scheme 2



2 4

2a: R^1=Ph, R^2=H, R^3=Me → 4a (100%, Method B)

2b: R^1=Ph, R^2=H, R^3=Et → 4b (98%, Method A)

2c: R^1=Ph, R^2=H, R^3=Isopropyl → 4c (79%, Method A)

2d: R^1=Me, R^2=H, R^3=Et → 4d (0%, Methods A and B)

2e: R^1=Me, R^2=H, R^3=Hexyl → 4e (40%, Method A)

2f: R^1=Me, R^2= $\begin{matrix}Me\\Me\end{matrix}$>C=CH$(CH_2)_2$-, R^3=Et → 4f (100%, Method B)

References

1. H. Ahlbrecht and C. Vonderheid, Synthesis, 512 (1975).

2. The starting materials (1) used in this work were synthesized according to the procedure reported in the literature [L. A. Yanovskaya, Ch. Shachidayatov, E. P. Prokofiev, G. M. Andrianova and V. F. Kucherov, Tetrahedron, 24, 4677 (1968)]. Physical properties of 1a obtained in 90% yield agreed with those reported in the literature described above.

1b: 36% yield; bp 70-72 °C/2 mmHg; ν_{CN} 2248 cm^{-1}; MS: m/e 166 (M^+); ^{1}H-NMR ($CDCl_3$/TMS) δ: 5.48 (d-d, 1H, J=15 Hz and 5 Hz), 6.10(d-q, 1H, J=15 Hz and 5 Hz).

1c: 70% yield; pale yellow oil; ν_{CN} 2220 cm^{-1}; MS: m/e 248 (M^+); ^{1}H-NMR ($CDCl_3$/TMS) δ: 5.10(b, 1H), 5.25(d, 1H, J=8 Hz).

^{1}H-NMR data shown are only for olefinic protones.

3. All α- and γ-alkylated products were viscous oil and new compounds. Their physical properties are as follows:

2a: yellow oil; ν_{CN} 2230 cm^{-1}; MS: m/e 242 (M^+); ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.14(d, 1H, J=15 Hz), 7.12(d, 1H, J=15 Hz).

2b: yellow oil; ν_{CN} 2230 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.10(d, 1H, J=15 Hz), 7.15(d, 1H, J=15 Hz).

2c: pale yellow oil; ν_{CN} 2245 cm^{-1}; MS: m/e 270 (M^+), 243 (M^+-HCN), 228 (M^+-C_3H_7); ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.06(d, 1H, J=17.5 Hz), 7.10(d, 1H, J=17.5 Hz).

2d: yellow oil; ν_{CN} 2240 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ: 5.26(d, 1H, J=15.5 Hz), 6.11(d-q, 1H, J= 15.5 Hz and 6 Hz).

2e: yellow oil; ν_{CN} 2235 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ: 5.32(d, 1H, J=15.5 Hz), 6.14(d-q, 1H, J= 15.5 Hz and 6 Hz).

2f: yellow oil; ν_{CN} 2230 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ: 5.03(b, 1H), 5.15(b, 1H).

3a: yellow oil; ν_{CN} 2215 cm^{-1}; MS: m/e 242 (M^+), 227 (M^+-Me); ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.08(d, 1H, J=10 Hz).

3b: yellow oil; ν_{CN} 2215 cm^{-1}; MS: m/e 256 (M^+), 227 (M^+-Et); ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.11(d, 1H, J=10 Hz).

3c: yellow oil; ν_{CN} 2210 cm^{-1}; MS: m/e 270 (M^+), 244 (M^+-CN), 227 (M^+-C_3H_7); ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.25(d, 1H, J=10 Hz).

^{1}H-NMR data shown are only for olefinic protones.

4. G. Büchi and H. Wüest, J. Am. Chem. Soc., 96, 7573 (1974).
5. G. Stork, A. A. Ozorio and A. Y. W. Leong, Tetrahedron Lett., 5175 (1978).
6. Within α,β-unsaturated ketones obtained in this work, physical properties of 4a and 4b agreed with those reported in the literatures [N. L. Drake and P. Allen, Jr., Org. Synth., Coll. Vol. 1, 77 (1967), and C. Harries and G. H. Muller, Chem. Ber., 35, 966 (1902)]. The corresponding ketone to 4d was not obtained in this work. Physical properties of other α,β-unsaturated ketones are as follows:

   4c: pale yellow oil; $\nu_{C=O}$ 1650 cm^{-1}; MS: m/e 174 (M^+), 131 (M^+-C_3H_7); ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.62(d, 1H, J=17 Hz), 7.48(d, 1H, J=17 Hz).

   4e: pale yellow oil; $\nu_{C=O}$ 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS) δ: 6.15(d, 1H, J=15.5 Hz), 6.88(d-q, 1H, J=15.5 Hz and 6 Hz).

   4f: coloreless oil; $\nu_{C=O}$ 1690 cm^{-1}; MS: m/e 180 (M^+), 165 (M^+-Me), 150 (M^+-2Me); ^{1}H-NMR ($CDCl_3$/TMS) δ: 5.28(b, 1H), 6.23(b, 1H).

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