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Regioselective Alkylation of Isopropylidene- and Cyclohexylidenepropanedinitrile with Phenacyl Bromides

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Abstract—Alkylation of isopropylidene- and cyclohexylidenepropanedinitrile with phenacyl bromides gave 2,2-bis(2-aryl-2-oxoethyl)propanedinitriles. Direct alkylation of propanedinitrile with phenacyl bromides afforded only 2-(2-aryl-2-oxoethyl)propanedinitriles.

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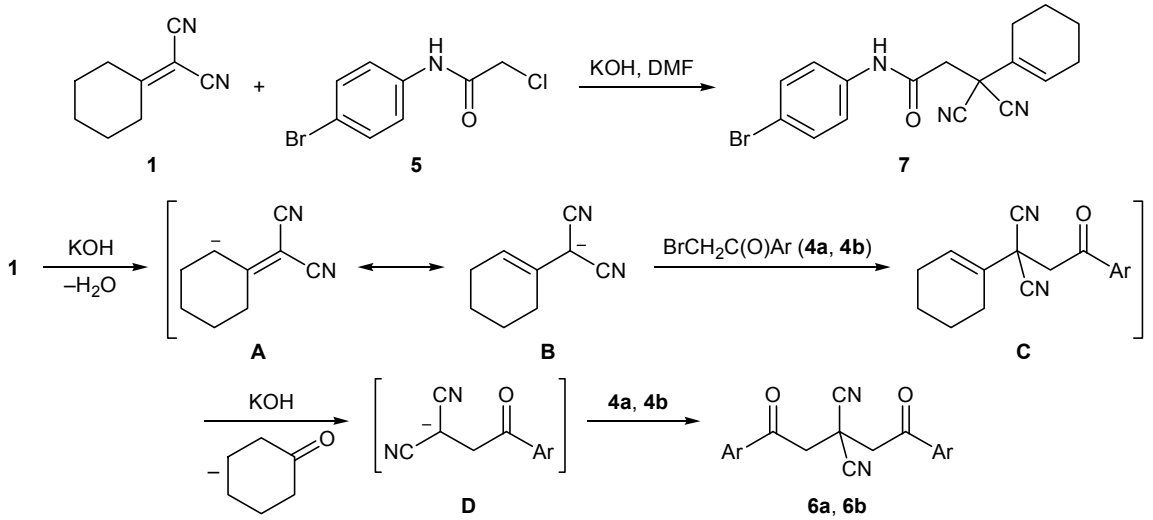
Cycloalkylidene- and isopropylidenepropanedinitriles are known to act as Michael acceptors, and this property was utilized in the synthesis of spiropyrans [1, 2] and dihydro- [3–5] and tetrahydropyridines [6, 7]. These compounds are also capable of undergoing dimerization in the presence of bases according to a Michael type reaction [8, 9], which suggests that they can also act as electron pair donors due to acidity of proton on the α-carbon atom with respect to the double bond.

Taking into account that the behavior of ylidenepropanedinitriles **1**–**3** as electron pair donors has been poorly studied, we were the first to examine their alkylation with phenacyl bromides **4a** and **4b** and *N*-(4-bromophenyl)-2-chloroacetamide (**5**) in DMF in the presence of aqueous potassium hydroxide. As a result, we isolated substituted propanedinitriles **6a** and **6b** and *N*-(4-bromophenyl)-3,3-dicyano-3-(cyclohex-1-en-1-yl)propanamide (**7**) (Schemes 1, 2).

A plausible reaction path includes deprotonation of **1** to carbanion **A** which may be represented by canonical structure **B**. Regioselective alkylation of the latter at the C^2 atom of the propanedinitrile fragment gives intermediate **C** whose alkaline hydrolysis leads to carbanion **D**. The subsequent alkylation of **D** with the second phenacyl bromide molecule yields final product **6**. Compounds **6a** and **6b** were also formed as the only products when the initial reactants **1**–**3** and **4** were

Scheme 1.



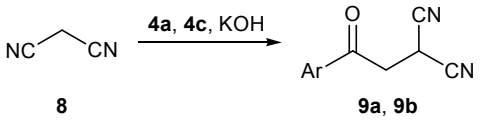
Ar = Ph (**a**), 4-ClC_6H_4 (**b**).

Scheme 2.

Ar = Ph (**a**), 4-ClC_6H_4 (**b**).

taken at a ratio of 1:1, but the best yields of **6** were obtained at a **1**–**3**-to-**4** ratio of 1:2. Thus, the second alkylation step is so fast that intermediate monoalkyl derivative **C** cannot be isolated. In contrast, the reaction of **1** with *N*-(4-bromophenyl)-2-chloroacetamide (**5**) afforded only the monoalkylation product, propanamide **7**. This result may be rationalized by reduced reactivity of chloroacetamides as alkylating agents compared to α-bromo ketones.

Scheme 3.



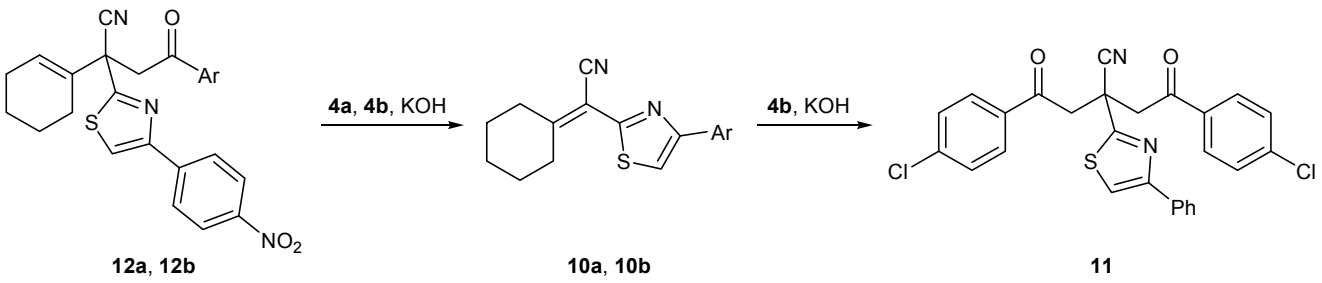
4, Ar = Ph (**a**), 4-BrC_6H_4 (**c**); **9**, Ar = Ph (**a**), 4-BrC_6H_4 (**b**).

Under analogous conditions, direct alkylation of propanedinitrile **8** with phenacyl bromides **4a** and **4c** afforded only previously reported [10, 11] monoalkylation products **9a** and **9b**, regardless of the reactant ratio (Scheme 3).

By alkylation of CH acid **10a** [12] with 2 equiv of 4-chlorophenacyl bromide **4b** we obtained substituted butanenitrile **11**, whereas cyclohexylideneacetonitrile **10b** reacted with an equimolar amount of **4a** or **4b** in DMF/KOH to give the corresponding monoalkyl derivative, 4-aryl-4-oxo-2-[4-(4-nitrophenyl-1,3-thiazol-2-yl)]-2-(cyclohex-1-en-1-yl)butanenitrile **12a** or **12b** (Scheme 4).

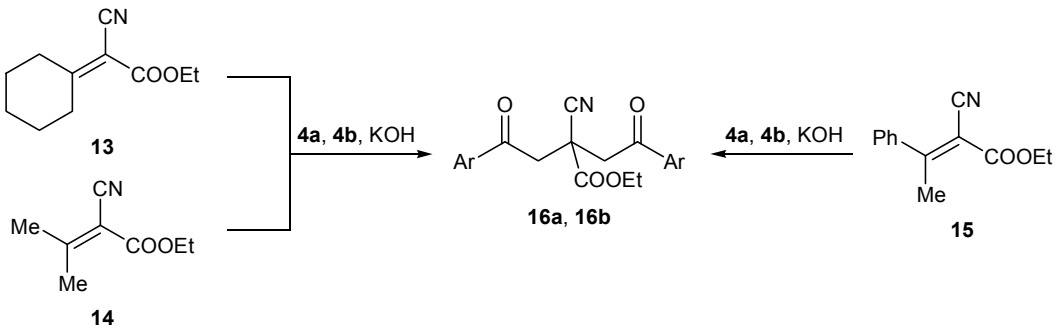
Substituted ethyl acrylates **13**–**15** were readily alkylated with phenacyl bromides **4a** and **4b** under analogous conditions with formation of ethyl cyanoacetates **16a** and **16b**; the highest yield of **16a** and **16b** was achieved with the use of 2 equiv of **4** (Scheme 5). Presumably, the reaction path is similar to that leading to compounds **6**.

Scheme 4.



10, Ar = Ph (**a**), 4-$O_2NC_6H_4$ (**b**); **12**, Ar = Ph (**a**), 4-ClC_6H_4 (**b**).

Scheme 5.



16, Ar = Ph (**a**), 4-ClC_6H_4 (**b**).

The structure of the isolated compounds was confirmed by spectral data. Their IR spectra contained absorption bands at 2235–2252 and 1666–1711 cm^{-1} due to stretching vibrations of the cyano and carbonyl groups, respectively. In the ^{13}C NMR spectra we observed signals from all carbon atoms present in their molecules. Compounds **7**, **11**, **12a**, **16a**, and **16b** displayed in the ^{1}H NMR spectra nonequivalence of methylene protons in the CH_2CO fragment (^{2}J = 16.8–18.2 Hz), indicating restricted rotation of the $ArCOCH_2$ substituent about the single carbon–carbon bond.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum One spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Varian-400 instrument at 400.13 and 100 MHz, respectively, from solutions in DMSO-d_6 containing tetramethylsilane as internal standard. The mass spectra were obtained on an Agilent 1100 LC/MSD SL instrument; samples were introduced in a CF_3COOH matrix. The elemental compositions were determined on a Perkin Elmer CHN analyzer. The melting points were measured on a Kofler hot stage. The progress of reactions was monitored, and the purity of the isolated compounds was checked, by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; spots were visualized under UV light or by treatment with iodine vapor.

Typical procedure for the alkylation of CH acids 1–3, 8, 10a, 10b, and 13–15. To a solution of 10 mmol of CH acid **1**–**3**, **8**, **10a**, **10b**, or **13**–**15** in 20 ml of DMF we added under stirring at 20°C 5.6 mL (10 mmol) of 10% aqueous potassium hydroxide and then 10 mmol of alkylating agent **4a**–**4c** or **5**. The mixture was stirred for 2 h and diluted with an equal volume of water, and the precipitate was filtered off and washed with water, ethanol, and hexane. In the synthesis of **6a**, **6b**, **11**, **16a**, and **16b**, 11.2 mL (20 mmol) of 10% aqueous potassium hydroxide and 20 mmol of phenacyl bromide **4a** or **4b** were used.

2,2-Bis(2-oxo-2-phenylethyl)propanedinitrile (6a) was synthesized from CH acid **1**, **2**, or **3** and phenacyl bromide (**4a**). Yield 78, 80, and 74%, respectively; yellow powder, mp 203–205°C (from EtOH). IR spectrum, ν, cm^{-1}: 2248 (C≡N), 1693 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.23 s (4H, CH_2), 7.57 t (4H, H_{arom}, J = 7.6 Hz), 7.68 t (2H, H_{arom}, J = 7.6 Hz), 8.02 d (4H, H_{arom}, J = 7.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.85, 44.55 (2C), 116.30 (2C), 128.54 (4C), 129.50 (4C), 134.82 (2C), 135.39 (2C), 194.40 (2C). Mass spectrum: m/z 301 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 75.33; H 4.55; N 9.16. $C_{19}H_{14}N_2O_2$. Calculated, %: C 75.48; H 4.67; N 9.27. M 302.336.

2,2-Bis[2-(4-chlorophenyl)-2-oxoethyl]propanedinitrile (6b). Yield 76 (from **1**), 8 (from **2**), 84% (from **3**); colorless powder, mp 250–252°C (from AcOH). IR spectrum, ν, cm^{-1}: 2251 (C≡N), 1698 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.22 s (4H, CH_2), 7.59 t (4H, H_{arom}, J = 8.6 Hz), 8.04 d (4H, H_{arom}, J = 8.6 Hz). Mass spectrum: m/z 370 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 61.32; H 3.14; N 7.40. $C_{19}H_{12}Cl_2N_2O_2$. Calculated, %: C 61.48; H 3.26; N 7.55. M 371.226.

***N*-(4-Bromophenyl)-3,3-dicyano-3-(cyclohex-1-en-1-yl)propanamide (7).** Yield 2.72 g (76%), colorless powder, mp 142–143°C (from EtOH). IR spectrum, ν, cm^{-1}: 3313 (NH), 2246 (C≡N), 1666 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.34–1.65 m (4H, CH_2), 1.76–2.19 m (4H, CH_2), 3.14 d and 3.48 d (1H each, CH_2CO, ^{2}J = 16.8 Hz), 6.10 br.s (1H, =CH), 7.28 d (2H, H_{arom}, J = 7.1 Hz), 7.70 d (2H, H_{arom}, J = 7.1 Hz), 9.27 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.11, 22.19, 22.02, 22.10, 23.27, 24.74, 47.94, 48.69, 126.86, 131.35 (2C), 132.25 (2C), 133.00, 158.37, 161.22, 171.64. Mass spectrum: m/z 357 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 56.91; H 4.42; N 11.60. $C_{17}H_{16}BrN_3O$. Calculated, %: C 57.00; H 4.50; N 11.73. M 358.241.

2-(2-Oxo-2-phenylethyl)propanedinitrile (9a). Yield 1.45 g (79%), colorless powder, mp 148–149°C (from EtOH). IR spectrum, ν, cm^{-1}: 2252 (C≡N), 1711 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.99 d (2H, CH_2, J = 6.0 Hz), 5.01 t (1H, CHCN, J = 6.0 Hz), 7.54 t (2H, H_{arom}, J = 7.5 Hz), 7.67 t (1H, H_{arom}, J = 7.5 Hz), 8.00 d (2H, H_{arom}, J = 7.6 Hz). Mass spectrum: m/z 183 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 71.62; H 4.29; N 15.14. $C_{11}H_8N_2O$. Calculated, %: C 71.73; H 4.38; N 15.21. M 181.199.

2-[2-(4-Bromophenyl)-2-oxoethyl]propanedinitrile (9b). Yield 2.16 g (82%), colorless powder, mp 99–100°C (from EtOH). IR spectrum, ν, cm^{-1}: 2249 (C≡N), 1698 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.98 d (2H, CH_2, J = 6.1 Hz), 5.01 t (1H, CHCN, J = 6.1 Hz), 7.71 d (2H, H_{arom}, J = 7.6 Hz), 7.93 d (2H, H_{arom}, J = 7.6 Hz). Mass spectrum: m/z 262 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 50.14; H 2.55; N 10.58. $C_{11}H_7BrN_2O$. Calculated, %: C 50.22; H 2.68; N 10.65. M 263.095.

4-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)-2-oxoethyl]-4-oxo-2-(4-phenyl-1,3-thiazol-2-yl)butanenitrile (11). Yield 2.5 g (70%), colorless powder,

mp 255–257°C (from BuOH). IR spectrum, ν, cm^{-1}: 2245 (C≡N), 1691 (C=O). ^1H NMR spectrum, δ, ppm: 4.19 d and 4.33 d (2H each, CH_2CO, ^2J = 18.2 Hz), 7.30 t (1H, Ph, J = 7.2 Hz), 7.34 t (2H, Ph, J = 7.5 Hz), 7.60 d (4H, H_{arom}, J = 8.2 Hz), 7.73 d (2H, Ph, J = 7.5 Hz), 7.99 d (4H, H_{arom}, J = 8.2 Hz), 8.09 s (1H, 5′-H). ^{13}C NMR spectrum, δ_C, ppm: 46.46 (2C), 50.11, 115.53, 118.14, 121.02, 125.98 (2C), 128.26 (2C), 128.73 (2C), 129.03 (2C), 130.06 (2C), 133.61 (2C), 134.59, 138.84, 147.12, 153.50, 160.11, 167.67, 182.08, 194.40 (2C). Mass spectrum, m/z 504 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 64.02; H 3.44; N 5.47. $C_{27}H_{18}Cl_2N_2O_2S$. Calculated, %: C 64.16; H 3.59; N 5.54. M 505.426.

2-(Cyclohex-1-en-1-yl)-2-[4-(4-nitrophenyl)-1,3-thiazol-2-yl]-4-oxo-4-phenylbutanenitrile (12a). Yield 3.23 g (73%), colorless powder, mp 160–162°C (from BuOH). IR spectrum, ν, cm^{-1}: 2235 (C≡N), 1689 (C=O). ^1H NMR spectrum, δ, ppm: 1.51–1.72 m (4H, CH_2), 1.96–2.22 m (4H, CH_2), 4.05 d and 4.40 d (1H each, CH_2CO, ^2J = 18.2 Hz), 6.11 br.s (1H, =CH), 7.54 t (2H, Ph, J = 7.5 Hz), 7.65 t (1H, Ph, J = 7.1 Hz), 8.03 d (2H, Ph, J = 7.5 Hz), 8.10 d (2H, H_{arom}, J = 8.3 Hz), 8.19 d (2H, H_{arom}, J = 8.3 Hz), 8.46 s (1H, 5′-H). ^{13}C NMR spectrum, δ_C, ppm: 21.19, 22.03, 24.18, 24.31, 37.22, 44.18, 46.02, 48.11, 121.02 (2C), 124.11 (2C), 127.15, 128.02 (2C), 128.93 (2C), 129.18 (2C), 133.18, 134.01, 140.00, 146.95, 168.30. Mass spectrum: m/z 442 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 67.60; H 4.35; N 9.32. $C_{25}H_{21}N_3O_3S$. Calculated, %: C 67.70; H 4.47; N 9.47. M 443.528.

4-(4-Chlorophenyl)-2-(cyclohex-1-en-1-yl)-2-[4-(4-nitrophenyl)-1,3-thiazol-2-yl]-4-oxobutanenitrile (12b). Yield 3.77 g (79%), colorless powder, mp 163–165°C (from EtOH). IR spectrum, ν, cm^{-1}: 2246 (C≡N), 1691 (C=O). ^1H NMR spectrum, δ, ppm: 1.48–1.66 m (4H, CH_2), 1.92–2.17 m (4H, CH_2), 6.09 br.s (1H, =CH), 7.62 d (2H, H_{arom}, J = 7.6 Hz), 8.06 d (2H, H_{arom}, J = 8.4 Hz), 8.11 d (2H, H_{arom}, J = 8.4 Hz), 8.25 d (2H, H_{arom}, J = 7.6 Hz), 8.52 s (1H, 5′-H). Mass spectrum: m/z 476 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 62.71; H 4.16; N 8.66. $C_{25}H_{20}ClN_3O_3S$. Calculated, %: C 62.82; H 4.22; N 8.79. M 477.973.

Ethyl 2-cyano-4-oxo-2-(2-oxo-2-phenylethyl)-4-phenylbutanoate (16a). Yield 2.86 g (82%, from **13**), colorless crystals, mp 134–136°C (from EtOH). IR spectrum, ν, cm^{-1}: 2248 (C≡N); 1710, 1693 (C=O). ^1H NMR spectrum, δ, ppm: 1.29 t (3H, Me, J = 7.0 Hz), 3.86 d and 3.99 d (2H each, CH_2CO, ^2J = 18.2 Hz), 4.22 q (2H, OCH_2, J = 7.0 Hz), 7.54 t (4H, Ph, J = 7.6 Hz), 7.66 t (2H, Ph, J = 7.2 Hz), 7.99 d (4H, Ph, J = 7.6 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.16, 41.91, 44.35 (2C), 62.88, 119.18, 128.55 (4C), 129.35 (4C), 134.47 (2C), 135.89 (2C), 168.57, 195.75 (2C). Mass spectrum: m/z 348 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 72.01; H 5.30; N 3.95. $C_{21}H_{19}NO_4$. Calculated, %: C 72.19; H 5.48; N 4.01. M 349.390.

Ethyl 4-(4-chlorophenyl)-2-[2-(4-chlorophenyl)-2-oxoethyl]-2-cyano 4-oxobutanoate (16b). Yield 2.93 g (70%, from **13**), colorless powder, mp 148–150°C (from EtOH). IR spectrum, ν, cm^{-1}: 2249 (C≡N); 1705, 1694 (C=O). ^1H NMR spectrum, δ, ppm: 1.19 t (3H, Me, J = 6.8 Hz), 3.89 d and 4.01 d (2H each, CH_2CO, ^2J = 18.2 Hz), 4.18 q (2H, OCH_2, J = 6.8 Hz), 7.64 d (4H, H_{arom}, J = 8.2 Hz), 8.10 d (4H, H_{arom}, J = 8.2 Hz). Mass spectrum: m/z 417 (I_{rel} 100%) $[M - 1]^+$. Found, %: C 60.18; H 3.96; N 3.22. $C_{21}H_{17}Cl_2NO_4$. Calculated, %: C 60.30; H 4.10; N 3.35. M 418.280.

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