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Reaction between 4-oxoalkane-1,1,2,2-tetracarbonitriles and morpholine: regioselective synthesis of 5-amino-2-(morpholin-4-yl)-3-(2-oxoalkyl)-3*H*-pyrrol-3,4-dicarbonitriles

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ABSTRACT

A new approach to the regioselective synthesis of polyfunctional 3*H*-pyrroles from 4-oxoalkane-1,1,2,2-tetracarbonitriles is described. 5-Amino-3-(2-aryl-2-oxoethyl)-3*H*-pyrrol-3,4-dicarbonitriles are prepared from 4-aryl-4-oxobutane-1,1,2,2-tetracarbonitriles. Diastereomeric 5-amino-2-morpholin-4-yl-3-(2-oxocyclohexyl)-3*H*-pyrrole-3,4-dicarbonitriles were obtained from 1-(2-oxocyclohexyl)ethane-1,1,2,2-tetracarbonitriles.

Being multifunctional compounds 4-oxoalkane-1,1,2,2-tetracarbonitriles[1] contain competitive reaction centers that enable them to take part in cascade transformations resulting in various classes of heterocyclic compounds. It has been reported that reactions of 4-oxoalkane-1,1,2,2-tetracarbonitriles with nitrogen-containing nucleophiles lead to amino-1,2-dicyano-4,6-diazabicyclo[3.2.1]oct-2-en-7-ones,[2a] 3-amidinio-2-aminopyridine-4-carboxylates,[2b] 4-aryl-1,1,2-tricyano-4-oxobut-2-en-1-ides,[2c] 3,4-dicyano-5,6,7,8-tetrahydroquinolin-2-olates,[2d] and cyclopenta[*b*]pyridines.[2e] Thus the regioselectivity of these processes depends on the reaction conditions and the nature of the initial compounds.

Vicinal cyano groups are the structural characteristics of 4-oxoalkane-1,1,2,2-tetracarbonitriles, which can take part in the formation of a pyrrole ring. In the case of systems with three substituents and one hydrogen atom a 3*H*-pyrrole ring should result.

Several synthetic methods for the preparation of 3*H*-pyrroles are known: cyclization of open-chain compounds,[3a–i] 1,3-dipolar cycloaddition,[3j] transformations of pyrrolidines,[3k–n] and anion-radical reactions.[3o,p] Some 3*H*-pyrroles were shown to exhibit antimicrobial or anticancer activity,[4] therefore the search for new efficient methods for their preparation is important.

Morpholine was employed as the nucleophilic reagent and the reaction of tetracarbonitriles **1a–f** proceeded to give exclusively, 5-amino-2-(morpholin-4-yl)-3-[2-oxoalkyl(cycloalkyl)]-3*H*-pyrrol-3,4-dicarbonitriles **2a–f** (Scheme 1, Table 1) in 79–93% yield.[5]

The structures of compounds **2a–f** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy and by mass spectrometry.[6] In the infrared spectra the intense stretching absorptions due to the carbonyl group were apparent at 1667–1691 cm^{-1} (for **2a–d**) and 1720–1723 cm^{-1} (for **2e,f**). The absorption band of the conjugated cyano group occurred at 2169–2182 cm^{-1}, the nonconjugated cyano group at 2230–2234 cm^{-1} and the amino group at 3149–3403 cm^{-1}. The ^{1}H NMR spectra showed specific chemical shifts for the protons of the amino group at 7.19–7.28 ppm and the morpholine fragment at 3.50–3.85 ppm. The morpholine protons appeared as typically broadened signals, especially for derivatives **2e,f**, while the corresponding resonances of compounds **2a–d** were only moderately broad. The appearance of the ^{1}H NMR signals can be explained by hindered rotation of the morpholine fragment, which is most evident in compounds **2e,f** due to the spatial arrangement of two sterically bulky substituents—the morpholine and cyclohexyl groups. The diastereotopic methylene protons adjacent to the C=O group in compounds **2a–c** appeared as two doublets with $^2J_{gem}$ = 17.7–17.8 Hz (AB spin system). The protons in compounds **2e,f** appeared as double signals due to the formation of a diastereomeric mixture with chiral centers at the R^2-group and nonconjugated β-CN group. The ^{1}H NMR spectrum of compound **2e** at 75 °C confirmed the presence of the diastereomeric pair, but at elevated temperature the signals of the morpholine protons were sharp and no longer broad. It should be mentioned that the

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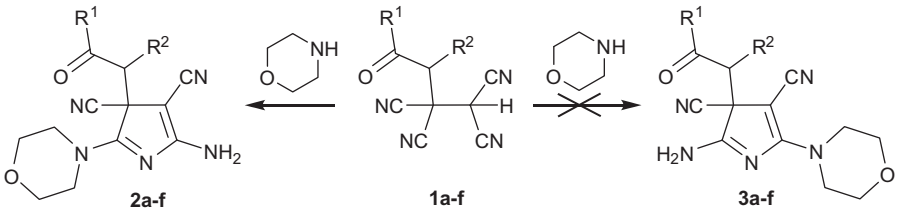


Scheme 1. Synthesis of 3*H*-pyrroles **2a**–**f**.

Table 1
Synthesis of 5-amino-2-morpholin-4-yl-3-[2-oxoalkyl(cycloalkyl)]-3*H*-pyrrol-3,4-dicarbonitriles **2a–f**

Carbonyl compound	R^1	R^2	Product	Yield[a] (%)
1a	C_6H_5	H	**2a**	93
1b	4-ClC_6H_4	H	**2b**	85
1c	4-$C_6H_5C_6H_4$	H	**2c**	91
1d	4-$CH_3OC_6H_4$	CH_3	**2d**	79
1e	–$(CH_2)_4$–		**2e**	88
1f	–$CH_2CH_2CH(t\text{-Bu})CH_2$–		**2f**	81

[a] Yield of isolated product.

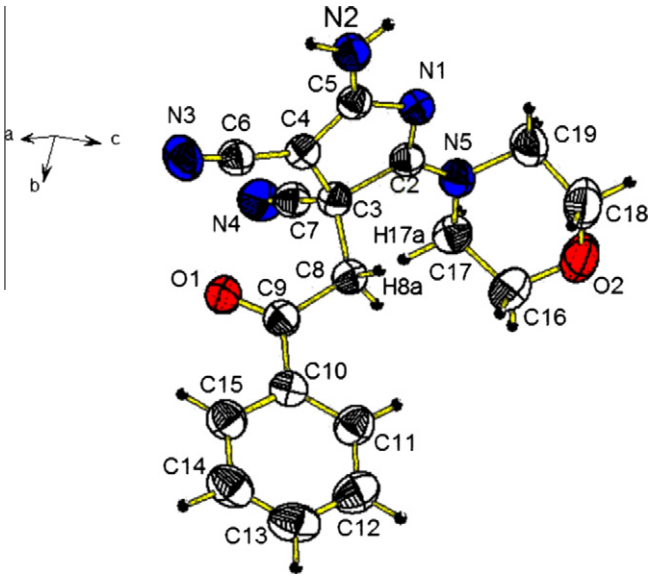


Figure 1. ORTEP diagram of compound **2a**.

methine proton adjacent to the C=O group in compounds **2e,f** occurred as a doublet of doublets with ^3J = 5.3–5.5 and 12.6–13.0 Hz indicating its axial orientation. In the ^{13}C NMR spectrum of compound **2a** the two cyano and carbonyl carbon atoms exhibited resonances at 117.56, 118.54, and 194.10 ppm, respectively, while the carbons neighboring the nitrogen atom in the 3*H*-pyrrole ring were detected as signals at 170.66 and 170.94 ppm. The mass spectra of all the products exhibited base peaks (m/z = 216) corresponding to the pyrrole fragment, while the molecular ion peaks had intensities in the range 3–72%.

An unambiguous determination of the position of the morpholine group was achieved by X-ray diffraction analysis using a single crystal of compound **2a** (Fig. 1).[7] The lone electron pair of nitrogen N5 conjugates with the π-system of the chain C2–N1–C5–N2, (the distance N5–C2 is 1.329(3) Å and C2–N1 is 1.310(3) Å) despite the repulsion of atoms H17a···H8a (the distance H17a···H8a is 2.10(3) Å, which is much less than the sum of the van der Waals radii of the hydrogen atoms). This latter fact indicates the essential difficulties associated with the substitution of H8a by any other functional group. In the crystal state, molecules form centrosymmetric dimers because of the N2–H2···N3i (*i*-symmetry code: 1−*x*, −*y*, −*z*;) hydrogen bonds.

The preparation of aryl-containing 3*H*-pyrroles **2a–d** was carried out at reduced temperature in ethyl acetate over 2–3 days, while the synthesis of compounds **2e,f** took 10–20 min in a solution of water and 2-propanol (10:1 by volume).

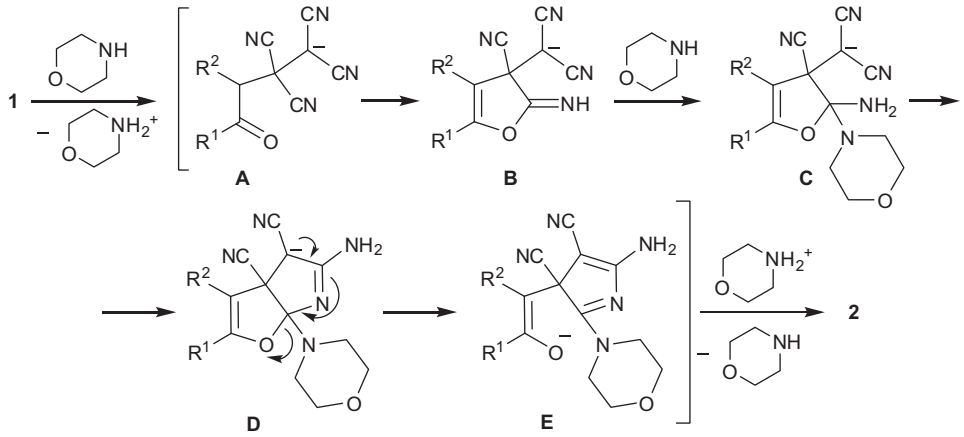
It is significant to note that all the mentioned reactions led exclusively to 3*H*-pyrroles **2**, but not to regioisomeric derivatives **3**. On the basis of this result, we assume that attack of the sufficiently bulky morpholine nucleophile is directed toward one of the β-cyano groups instead of the more sterically accessible terminal cyano groups. In the substrates the β-cyano groups are surrounded by two bulky fragments, the carbonyl, and dicyanomethyl groups, therefore direct attack of morpholine is very difficult. Keeping this fact in mind the following inferences can be made: (1) the terminal cyano groups are deactivated; (2) the carbonyl group takes part in the transformations. A possible mechanism for this transformation is depicted in Scheme 2.

In the first stage, morpholine possibly acts as a base and forms a salt with the CH-acidic center of the substrate. Previously the synthesis of similar salts with ammonia had been carried out in ethyl acetate.[2c] It is also known that tetracyanoalkanes are able to form salts with metal cations.[8] The negative charge on these salts is obviously delocalized on the dicyanomethine fragment and reduces the electrophilic properties of the terminal cyano groups, which are thereby deactivated. This is the reason why 3*H*-pyrroles **3** do not form.

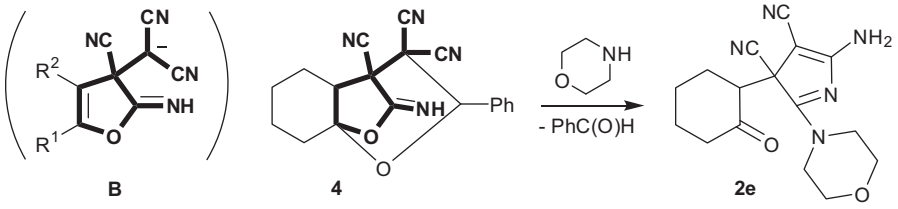
Tetracyanoalkanone derivatives are able to transform into compounds with an iminofuran fragment under basic conditions, for example, in reactions with sodium borohydride[2f] or pyridine.[2g] Therefore, we assume that ketonitrile salts **A** transform into iminofuran derivatives **B**. The reaction of amines with imino esters is an example of Pinner amidine synthesis,[9] and proceeds via addition to the imine fragment and leads to intermediate **C**. The next stage is the formation of pyrrole **D**. The synthesis of structurally analogous furo[2,3-*b*]pyrroles had earlier been realized from tetracyanoalkanes by the treatment with sodium borohydride.[2f] Finally the intermediate **D** undergoes ring-opening of the furan moiety with the formation of **E**, which is further transformed into product **2**.

To prove the formation of 3*H*-pyrroles **2** proceeds through the intermediate **B** we synthesized its structural analog, 12-imino-9-phenyl-10,11-dioxatricyclo[5.3.2.$0^{1,6}$]dodecane-7,8,8-tricarbonitrile **4**[2h] and treated it with morpholine under similar conditions. The reaction resulted in 5-amino-2-(morpholin-4-yl)-3-(2-oxocyclohexyl)-3*H*-pyrrol-3,4-dicarbonitrile (**2e**) (Scheme 3) in 82% yield.

In conclusion, an example of a new synthetic method for the preparation of polyfunctional 3*H*-pyrroles via cyclization of vicinal dinitrile-containing compounds has been demonstrated. The simplicity, high yields, and regiospecificity of the procedure described make it attractive for further investigation. The scope of this chemistry will be investigated by the variation of the initial nitriles and nucleophilic components.



Scheme 2. A possible mechanism for the formation of 3*H*-pyrroles **2**.



Scheme 3. Cross-synthesis of 3*H*-pyrrole **2e**.

Acknowledgment

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5. *Typical procedure for the preparation of 5-amino-2-morpholin-4-yl-3-(2-aryl-2-oxo)-3H-pyrrole-3,4-dicarbonitriles* ***2a–d***. To a stirred solution of the appropriate 4-aryl-4-oxobutane-1,1,2,2-tetracarbonitrile **1a–d** (0.5 mmol) in dry EtOAc (3 ml) at −5 to −10 °C was added morpholine (1 mmol) and the reaction mixture became yellow-orange in color. After 2–3 d at −5 to −10 °C the precipitated light-yellow solid was filtered, washed sequentially with cold EtOAc (2 ml) and Et_2O (1 ml) and dried. *Typical procedure for the preparation of 5-amino-2-morpholin-4-yl-3-(2-oxocyclohexyl)-3H-pyrrole-3,4-dicarbonitriles* ***2e,f***. To a stirred suspension of the appropriate 1-(2-oxocyclohexyl)ethane-1,1,2,2-tetracarbonitrile **1e,f** (0.5 mmol) in a 10:1 mixture of H_2O and *i*PrOH (5 ml) was added morpholine (1 mmol) and the reaction mixture became transparent yellow in color. After stirring at room temperature for 15–30 min the newly precipitated solid was filtered, washed sequentially with H_2O (5 ml) and *i*PrOH (2 ml). The isolated products were purified by crystallization from *i*PrOH and dried.
6. *Analytical data for compounds* ***2a–f***. *Compound* ***2a***. mp 208–209 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 3.62–3.80 (8H, m, morpholine), 3.92 (1H, d, J = 17.8 Hz, CH_2CO), 4.06 (1H, d, J = 17.8 Hz, CH_2CO), 7.27 (2H, s, NH_2), 7.53–7.57 (2H, m, 2-*m*-H-Ar), 7.67–7.70 (1H, m, 1-*p*-H-Ar), 7.98–8.01 (2H, m, 2-*o*-H-Ar). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 42.73, 47.45, 57.54, 65.98, 117.56, 118.54, 128.66, 129.17, 134.24, 136.17, 170.66, 170.94, 194.10. IR (mineral oil, cm^{-1}) 3184–3311 (NH_2), 2232, 2182 (C≡N), 1691 (C=O). MS (EI, 70 eV): m/z (%) 335 (M^+, 72), 216 (100). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.57; H, 5.02; N, 20.97. *Compound* ***2b***. mp 220–221 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 3.66–3.78 (8H, m, morpholine), 3.90 (1H, d, J = 17.7 Hz, CH_2CO), 4.06 (1H, d, J = 17.7 Hz, CH_2CO), 7.26 (2H, s, NH_2), 7.61–7.64 (2H, m, $H^{3,5}$-Ar), 7.99–8.03 (2H, m, $H^{2,6}$-Ar). IR (mineral oil, cm^{-1}) 3157–3403 (NH_2), 2233, 2172 (C≡N), 1667 (C=O). MS (EI, 70 eV): m/z (%) 369 (M^+, 3), 216 (100). Anal. Calcd for $C_{18}H_{16}ClN_5O_2$: C, 58.46; H, 4.36; N, 18.94. Found: C, 58.53; H, 4.31; N, 19.02. *Compound* ***2c***. mp 229–230 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 3.67–3.79 (8H, m, morpholine), 3.96 (1H, d, J = 17.7 Hz, CH_2CO), 4.10 (1H, d, J = 17.7 Hz, CH_2CO), 7.29 (2H, s, NH_2), 7.43–7.46 (1H, m, Ar), 7.50–7.54 (2H, m, Ar), 7.74–7.79 (2H, m, Ar), 7.82–7.87 (2H, m, Ar), 8.04–8.10 (2H, m, Ar). IR (mineral oil, cm^{-1}) 3167–3401 (NH_2), 2234, 2179 (C≡N), 1668 (C=O). MS (EI, 70 eV): m/z (%) 411 (M^+, 3), 216 (100). Anal. Calcd for $C_{24}H_{21}N_5O_2$: C, 70.06; H, 5.14; N, 17.02. Found: C, 69.89; H, 5.18; N, 17.13. *Compound* ***2d***. mp 211–212 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.98 (3H, d, J = 6.9 Hz, CH_3), 3.68–3.76 (8H, m, morpholine), 3.86 (3H, s, OCH_3), 4.26 (1H, q, J = 6.9 Hz, C*H*CH_3), 7.08 (2H, d, J = 8.9 Hz, $H^{3,5}$-Ar), 7.28 (2H, s, NH_2), 8.00 (2H, d, J = 8.9 Hz, $H^{2,6}$-Ar). IR (mineral oil, cm^{-1}) 3149–3347 (NH_2), 2233, 2169 (C≡N), 1672 (C=O). MS (EI, 70 eV): m/z (%) 379 (M^+, 5), 216 (100). Anal. Calcd for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.33; H, 5.51; N, 18.52. *Compound* ***2e***. mp 195–196 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 1.24–2.42 (8H, m, $4CH_2$), 3.43 (1H, dd, J = 5.5, 12.6 Hz CHCO); 3.50–3.85 (8H, m, morpholine), 7.19*, 7.27 (2H, s, NH_2). ^{1}H NMR (500.13 MHz, DMSO-d_6, 348 K): δ 1.28–2.38 (8H, m, $4CH_2$), 3.37 (1H, dd,

J = 5.7, 12.5 Hz CHCO), 3.50 (1H, dd, J = 5.6, 12.4 Hz CHCO), 3.60–3.80 (8H, m, morpholine), 6.86*, 6.95 (2H, s, NH_2). IR (mineral oil, cm^{-1}) 3174–3324 (NH_2), 2230, 2174 (C≡N), 1719 (C=O). MS (EI, 70 eV): m/z (%) 313 (M^+, 24), 216 (100). Anal. Calcd for $C_{16}H_{19}N_5O_2$: C, 61.33; H, 6.11; N, 22.35. Found: C, 61.45; H, 6.02; N, 22.42. *Compound* ***2f***. mp 125–126 °C; ^1H NMR (500.13 MHz, DMSO-d_6): δ 0.91, 0.93* (9H, s, *t*-Bu), 1.05–2.80 (7H, m, $3CH_2$+CH), 3.47 (1H, dd, J = 5.3, 13.0 Hz, CHCO), 3.55–3.80 (8H, m, morpholine), 7.20, 7.26* (2H, s, NH_2). IR (mineral oil, cm^{-1}) 3183–3354 (NH_2), 2234, 2179 (C≡N), 1723 (C=O). MS (EI, 70 eV): m/z (%) 369 (M^+, 3), 216 (100). Anal. Calcd for $C_{20}H_{27}N_5O_2$: C, 65.02; H, 7.37; N, 18.96. Found: C, 65.11; H, 7.30; N, 19.01; *refers to signals of the diastereoisomers.

7. Crystallographic data (excluding structure factors) for the structure **2a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 804729. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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