Reaction of 3-aminocyclohex-2-en-1-ones with arylidenemalononitriles: synthesis of N-substituted 1,4,5,6,7,8-hexahydroquinolin-5-ones

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Dedicated to Professor M. G. Voronkov on the occasion of his 80th birthday
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Abstract
The reaction of 3-amino- and 3-hydrazinocyclohex-2-en-1-ones derived from cyclohexane-1,3-diones and an appropriate amine or hydrazine with 2-arylidenedemalononitriles was investigated. An efficient method for the synthesis of N-substituted 1,4,5,6,7,8-hexahydroquinolin-5-ones was elaborated.

Keywords: 3-Aminocyclohex-2-en-1-ones, 3-hydrazinocyclohex-2-en-1-ones, 2-arylidenedemalononitriles, 1,4,5,6,7,8-hexahydroquinolin-5-ones

Introduction

1,4-Dihydropyridines have received considerable attention because of their pivotal role in various biological processes. Numerous derivatives of dihydropyridines have been reported to have wide biological activity, e.g. being used in the treatment of cardiovascular disease (calcium antagonist). This applies especially to 4-aryl- or hetaryl-substituted 1,4-dihydropyridines. One of the well-known cardiovascular agents of this kind is Nifedipine 1.

![Chemical Structure of Nifedipine](image)

It is conceivable that fused 1,4-dihydropyridines of type 2 with different substituents R at
the ring nitrogen atom are also of considerable practical and theoretical interest. However, these compounds are scarcely studied, and there are only a few publications\(^3,4\) on their synthesis involving the reaction of cyclic enaminoketones 3 with arylidene derivatives of malononitrile 4. This method allows the attachment of substituents to the nitrogen atom in the course of the preparation of the enaminoketones 3. It has been shown that heating of 3-anilino-5,5-dimethylcyclohex-2-en-1-one 3a with 2-benzylidenemalononitrile 4a in alcohol and in the presence of catalytic amounts of a base yields the N-phenyl-substituted hexahydroquinoline 5a (Scheme 1).\(^3\)

\[
\begin{align*}
\text{Scheme 1} \\
\end{align*}
\]

Recently, we have extended this approach to the reaction of 3-(2-phenyl-hydrazino)cyclohex-2-en-3-one 3b with 2-(4-bromobenzylidene)malononitrile 4b.\(^4\) The product of this reaction, the N-(phenylamino)hexahydroquinoline derivative 5b was found to undergo an interesting diastereoselective rearrangement forming the previously unknown heterocyclic system 6 with partially hydrogenated fused indole and pyridine moieties\(^5\) (Scheme 2).

\[
\begin{align*}
\text{Scheme 2} \\
\end{align*}
\]

The present paper presents the results of a somewhat extended investigation of the condensation of N-substituted and N-unsubstituted 3-aminocyclohex-2-en-1-ones 3 with 2-arylidemalononitriles 4 resulting in 4-aryl-substituted hexahydroquinolin-5-ones 4 with various substituents at the ring nitrogen atom. The optimal reaction conditions for the conversion
for each type of 3-aminocyclohex-2-en-1-one 3 have been elaborated.

**Results and Discussion**

The N-unsubstituted 3-aminocyclohex-2-en-1-one 3c readily reacted with 2-benzylidene-

\[ \text{malononitrile 4a} \] upon short heating of a benzene solution in the presence of catalytic amounts of 

piperidine and afforded the N-unsubstituted hexahydroquinoline derivative 5c. The reaction proceeded in two steps: Heating the mixture of the reactants without a base catalyst yielded the 

adduct 7, which was isolated and identified. Only in the presence of a base (piperidine) the 

intramolecular cyclization was induced leading to the hexahydroquinolin-5-one 5c (Scheme 3).

![Scheme 3]

\[ \text{N-Aryl substituents decrease the nucleophilicity of enaminoketones 3 toward 2-arylidene-} \]

\[ \text{malononitriles 4; a base catalyst was required to achieve the formation of the N-phenyl-} \]

\[ \text{substituted hexahydroquinoline 5a} \] Presumably, the base generates the anion of the 3-amino-

\[ \text{cyclohex-2-en-1-one 3a, thus facilitating the addition to the unsaturated nitrile 4a (Scheme 4).} \]

![Scheme 4]

Unlike the N-phenyl derivative 3a the N-alkyl-substituted 3-aminocyclohex-2-en-1-one 3d 

did not require a base to react with 2-(4-chlorobenzylidene)malononitrile 4c giving rise to the 

formation of the N-(n-pentyl)-substituted hexahydroquinoline 5d (Scheme 5). The electron-

donating character of the N-alkyl substituent increases the nucleophilicity of the enaminoketone.

![Scheme 5]
Similarly, the 3-aminocyclohex-2-en-1-one 3e (derived from cyclohexane-1,3-dione and N,N-dimethylhydrazine) readily reacted with 2-(4-bromobenzylidene)malononitrile 4b yielding the N-dimethylamino-substituted hexahydroquinolin-5-one 5e (Scheme 1). Also in this case a base was dispensable due to the increased nucleophilicity of the enehydrazinoketone. This is analogous to the earlier reported reaction of the N-arylhydrazine derivative 3b with 2-(4-bromobenzylidene)malononitrile 4b giving rise to the formation of the N-anilino-substituted hexahydroquinolin-5-one 5b (Scheme 2).

These results can be summarized as follows: 3-Hydrazinocyclohex-2-en-1-ones like 3b and 3e readily reacted with 2-(4-bromobenzylidene)malononitrile 4b and afforded 1,2-diamino-substituted hexahydroquinolin-5-ones 5b and 5e, respectively. The N-unsubstituted and the N-alkyl-substituted 3-aminocyclohex-2-en-1-ones 3c and 3d also did not require a base to react with 2-arylidenedmalononitriles 4a and 4c; whereas 3d was converted directly into the corresponding 2-aminohexahydroquinolin-5-one 5d, the conversion of the isolated adduct 7 (from 3c and 4a) into the cyclic product 5e was achieved only after addition of a base catalyst. The 3-anilinocyclohex-2-en-1-one derivative 3a required a base to start the reaction with 2-benzylidenemalononitrile 4a.

![Scheme 6](image)

Scheme 6

The reaction of 3-aminocyclohex-2-en-1-ones with an N-substituent bearing a functional group as in 3f and 3g can induce a subsequent intramolecular cyclization reaction of the apparently first-formed 2-aminohexahydroquinoline product 5. Enaminoketone 3f (prepared from glycine ethyl ester and dimedone) was allowed to react with the 2-(3-nitrobenzylidene)malononitrile 4d. The expected reaction product, the 2-aminohexahydroquinoline derivative 5f was not isolated; instead, the product obtained turned out to be the imidazo[1,2-a]quinoline derivative 8, obviously resulting from the additional cyclization of the presumed precursor 5f involving the ester and 2-amino groups (Scheme 6).

The N-aryl-substituted 3-aminocyclohex-2-en-1-one 3g (prepared from dimedone and 2-aminobenzonitrile) required base catalysis (DBU) to promote the reaction with 2-(2,4-dichlorobenzylidene)malononitrile 4e; the product, quinolino[1,2-a]quinazoline derivative 9 obviously results from the cyclization of the 2-amino and 1-(2-cyanophenyl) functionalities of the presumed precursor 5g (Scheme 7).
Experimental Section

General Procedures. All reagents are commercially available (Aldrich, Merck) and were used without further purification. Thin-layer chromatography (TLC, on aluminium plates coated with silica gel 60F254, 0.25 mm thickness, Merck) was used for monitoring the reactions; eluent hexane/ethyl acetate 1:3. Melting points (mp) were determined on a Kofler hot stage microscope. 1H and 13C NMR spectra of DMSO-d6 solutions were recorded with a Bruker AM-300 instrument.

The enamino ketones 3c, 3d, 3e, 3g were prepared from the corresponding cyclohexa-1,3-diones and amines or hydrazines according to procedures described in the literature. 2-Aryldienemalononitriles 4a, 4b, 4c, 4d, 4e were prepared from the corresponding aromatic aldehydes and malononitrile according to procedures reported in the literature.

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5c). To a solution of 3c (0.28 g, 2 mmol) and 4a (0.31 g, 2 mmol) in refluxing benzene (6 mL) a few drops of piperidine were added; the resulting mixture was refluxed for 30 min. Then the reaction mixture was cooled, the precipitate formed was filtered off and washed on the filter funnel with a small amount of benzene. Recrystallization from a small amount of ethanol gave 5c (0.44 g, 75%) as colorless crystals, mp 265–267 °C. 1H NMR (300 MHz): δ 0.85 (3H, s, CH3), 1.05 (3H, s, CH3), 2.00 (1H, d, J = 18 Hz, CH2), 2.20 (1H, d, J = 18 Hz, CH2), 2.30–2.50 (2H, m, CH2), 4.30 (1H, s, CH), 5.60 (2H, s, NH2), 7.10–7.35 (5H, m, CHAr), 8.80 (1H, s, NH). Anal. Calcd for C18H19N3O (293.37): C, 73.70; H, 6.53; N, 14.32. Found: C, 73.93; H, 6.78; N, 14.11.

2-[(2-Amino-4,4-dimethyl-6-oxo-1-cyclohexenyl)(phenyl)methyl]malononitrile (7). A solution of 3c (0.28 g, 2 mmol) and 4a (0.31 g, 2 mmol) in benzene (6 mL) was refluxed for 30 min. Then the reaction mixture was cooled, the precipitate formed was filtered off and washed on the filter funnel with a small amount of benzene affording colorless crystals 7 (0.50 g, 85%), mp 213–215 °C. 1H NMR (300 MHz): δ 0.85 (3H, s, CH3), 1.00 (3H, s, CH3), 2.00 (2H, s, CH2), 2.30 (2H, s, CH2), 4.50 (1H, d, J = 14 Hz, CH), 6.10 (1H, d, J = 14 Hz, CH), 7.20–7.50 (7H, m,
\[ \text{CHPh, NH}_2 \]. 13C NMR (75 MHz): \[ \delta 25.85 (\text{CH}), 26.82 (\text{CH}_3), 28.22 (\text{CH}_3), 31.53 (\text{CMe}_2), 41.91 (\text{CH}), 42.89 (\text{CH}_2), 50.59 (\text{CH}_2), 102.55 (\text{C=CH-NH}_2), 114.45 (\text{CN}), 114.69 (\text{CN}), 127.13 (\text{CHPh}), 127.95 (\text{CHPh}), 128.08 (\text{CHPh}), 139.21 (\text{CHMe}), 163.30 (\text{C=NH}_2), 193.51 (\text{CO}) \]. Anal. Calcd for \[ \text{C}_{18}\text{H}_{19}\text{N}_3\text{O} \] (293.37): C, 73.70; H, 6.53; N, 14.32. Found: C, 73.44; H, 6.37; N, 14.66.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-pentyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5d). A solution of 3d (0.42 g, 2 mmol) and 4c (0.38 g, 2 mmol) in benzene (10 mL) was refluxed for 4 h. Then the reaction mixture was cooled, and solvent was evaporated under reduced pressure. Recrystallization from a small amount of ethanol gave colorless crystals 5d (0.63 g, 79%), mp 255–256 °C. 1H NMR (300 MHz): \[ \delta 0.80 (3\text{H}, \text{t, CH}_3), 0.95 (3\text{H}, \text{s, CH}_3), 1.05 (3\text{H}, \text{s, CH}_3), 1.10–1.30 (4\text{H}, \text{m, CH}_2), 1.40–1.55 (2\text{H}, \text{m, CH}_2), 2.10–2.25 (2\text{H}, \text{m, CH}_2), 2.40 (1\text{H}, \text{d, } J = 18 \text{ Hz, CH}_2), 2.65 (1\text{H}, \text{d, } J = 18 \text{ Hz, CH}_2), 3.60 (1\text{H}, \text{m, CH}_2), 3.80 (1\text{H}, \text{m, CH}_2), 4.45 (1\text{H}, \text{s, CH}), 6.00 (2\text{H}, \text{s, NH}_2), 7.10 (2\text{H}, \text{d, } J = 8 \text{ Hz, CH}_2), 7.30 (2\text{H}, \text{d, } J = 8 \text{ Hz, CH}_2). \] Anal. Calcd for \[ \text{C}_{23}\text{H}_{28}\text{ClN}_3\text{O} \] (397.95): C, 69.42; H, 7.09; Cl, 8.91; N, 10.56. Found: C, 69.58; H, 7.01; Cl, 8.77; N, 10.42.

Ethyl 2-[(5,5-dimethyl-3-oxo-1-cyclohexenyl)amino]acetate (3f). Triethylamine (2.02 g, 0.02 mol) was added to a solution of dimedone (2.8 g, 0.02 mol) and glycine ethyl ester hydrochloride (2.79 g, 0.02 mol) in chloroform (70 mL); the reaction mixture was stirred at room temperature for 48 h. Then the chloroform solution was washed with water and dried over \( \text{MgSO}_4 \). After removal of the solvent the crude product was recrystallized from the mixture ethyl acetate/heptane to give colorless crystals of 3f (3.17 g, 70%), mp 87–88 °C. 1H NMR (300 MHz): \[ \delta 1.00 (6\text{H}, \text{s, CH}_3), 1.20 (3\text{H}, \text{t, } J = 7 \text{ Hz, CH}_3\text{CH}_2), 1.95 (2\text{H}, \text{s, CH}_2), 2.20 (2\text{H}, \text{s, CH}_2), 3.85 (2\text{H}, \text{d, } J = 6 \text{ Hz, CH}_2), 4.15 (2\text{H}, \text{q, } J = 7 \text{ Hz, CH}_3\text{CH}_2), 4.70 (1\text{H}, \text{s, CH}), 7.10 (1\text{H}, \text{br t, } J = 6 \text{ Hz, NH}) \]. Anal. Calcd for \[ \text{C}_{12}\text{H}_{19}\text{NO}_3 \] (225.29): C, 63.98; H, 8.50; N, 6.22. Found: C, 64.14; H, 8.39; N, 6.06.

8,8-Dimethyl-2,6-dioxo-5-(3-nitrophenyl)-1,2,3,5,6,7,8,9-octahydroimidazo[1,2-\text{a}]quinoline-4-carbonitrile (8). A solution of 3f (0.45 g, 2 mmol) and 4d (0.40 g, 2 mmol) in benzene (8 mL) was refluxed for 8 h. Then the reaction mixture was cooled, the separated precipitate was filtered off and washed on the filter funnel with small amounts of benzene and ethanol yielding yellow crystals 8 (0.61 g, 72%), mp >320 °C. 1H NMR (300 MHz): \[ \delta 1.00 (6\text{H}, \text{s, CH}_3), 1.20 (3\text{H}, \text{t, } J = 7 \text{ Hz, CH}_3\text{CH}_2), 1.95 (2\text{H}, \text{s, CH}_2), 2.20 (2\text{H}, \text{s, CH}_2), 3.85 (2\text{H}, \text{d, } J = 6 \text{ Hz, CH}_2), 4.15 (2\text{H}, \text{q, } J = 7 \text{ Hz, CH}_3\text{CH}_2), 4.70 (1\text{H}, \text{s, CH}), 7.10 (1\text{H}, \text{br t, } J = 6 \text{ Hz, NH}) \]. 13C NMR (75 MHz): \[ \delta 26.21 (\text{CH}_3), 29.26 (\text{CH}_3), 31.73 (\text{CHMe}_2), 37.32 (\text{CH}), 38.19 (\text{CH}_2), 48.85 (\text{CH}_2), 49.43 (\text{CH}_2), 62.58 (3\text{C}), 108.33 (5\text{C}), 117.82 (\text{CN}), 121.56 (\text{CH}_2), 121.68 (\text{CH}_2), 129.88 (\text{CH}_2), 134.22 (\text{CH}_2), 147.62 (\text{C}_4\text{N}_2\text{O}_2), 147.73 (\text{C}_4\text{H}_2), 149.06 (2\text{C}), 149.17 (6\text{C}), 170.15 (\text{NCO}), 193.79 (\text{CO}) \]. Anal. Calcd for \[ \text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4 \] (378.39): C, 63.49; H, 4.79; N, 14.81. Found: C, 63.81; H, 4.87; N, 14.68.

5-Amino-8-(2,4-dichlorophenyl)-11,11-dimethyl-9-oxo-9,10,11,12-tetrahydro-8H-quinolino-[1,2-\text{a}]quinazoline-7-carbonitrile (9). To a refluxing solution of 3g (0.48 g, 2 mmol) and 4e (0.45 g, 2 mmol) in ethanol (7 mL) a few drops of DBU were added. The reaction mixture was refluxed for 5 h, then cooled; the separated precipitate was filtered off, washed on the filter...
funnel with ethanol affording yellow crystals \(9\) (0.66 g, 71%), mp >320 °C. \(^1H\) NMR (300 MHz): \(\delta\) 0.90 (3H, s, CH\(_3\)), 1.10 (3H, s, CH\(_3\)), 2.20 (2H, d, \(J = 18\) Hz, CH\(_2\)), 2.50 (1H, d, \(J = 18\) Hz, CH\(_2\)), 3.55 (1H, d, \(J = 18\) Hz, CH\(_2\)), 5.15 (1H, s, CH), 7.10 (1H, d, \(J = 8\) Hz, CH\(_{Ar}\)), 7.25 (1H, d, \(J = 8\) Hz, CH\(_{Ar}\)), 7.35 (1H, m, CH\(_{Ar}\)), 7.50–7.80 (3H, m, CH\(_{Ar}\)), 8.00 (1H, d, \(J = 8\) Hz, CH\(_{Ar}\)), 8.10 (2H, br s, NH\(_2\)). Anal. Calcd for C\(_{25}H_{20}Cl_2N_4O\) (463.37): C, 64.80; H, 4.35; Cl, 15.30; N, 12.09. Found: C, 64.52; H, 4.27; Cl, 15.54; N, 12.31.

2-Amino-4-(4-bromophenyl)-1-(dimethylamino)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (5e). \(^4\) A solution of 3e (0.31 g, 2 mmol) and 4b (0.47 g, 2 mmol) in 5 mL of ethanol was refluxed for 3 h. Then the reaction mixture was cooled, the precipitate that formed was filtered off and washed on the filter funnel with a small amount of ethanol. The product 5e (0.55 g, 71%) was obtained as a colorless crystals, mp 237–238 °C. \(^1H\) NMR (300 MHz): \(\delta\) 1.60–2.30 (4H, m, 2CH\(_2\)), 2.60–2.75 (2H, m, CH\(_2\)), 2.85 (3H, s, NCH\(_3\)), 2.90 (3H, s, NCH\(_3\)), 4.30 (1H, s, CH), 6.35 (2H, s, NH\(_2\)), 7.05 (2H, d, \(J = 8\) Hz, CH\(_{Ar}\)), 7.45 (2H, d, \(J = 8\) Hz, CH\(_{Ar}\)). \(^13C\) NMR (75 MHz): \(\delta\) 20.87 (CH\(_2\)), 25.21 (CH\(_2\)), 35.44 (CH), 36.18 (CH\(_2\)), 43.29 (NCH\(_3\)), 44.47 (NCH\(_3\)), 56.99 (3-C), 112.37 (5-C), 119.19 (C\(_{ArBr}\)), 121.76 (CN), 128.92 (CH\(_{Ar}\)), 131.22 (CH\(_{Ar}\)), 146.15 (CAr), 153.04 (2-C), 156.31 (6-C), 193.79 (CO). Anal. Calcd for C\(_{18}H_{19}BrN_4O\) (387.28): C, 55.83; H, 4.95; Br, 20.63; N, 14.47. Found: C, 55.59; H, 5.09; Br, 20.79; N, 14.32.

References and Notes