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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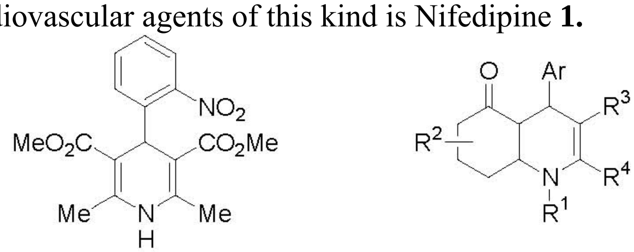
Abstract
The reaction of 3-amino- and 3-hydrazinocyclohex-2-en-1-ones derived from cyclohexane-1,3-diones and an appropriate amine or hydrazine with 2-arylidenemalononitriles was investigated. An efficient method for the synthesis of *N*-substituted 1,4,5,6,7,8-hexahydroquinolin-5-ones was elaborated.

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

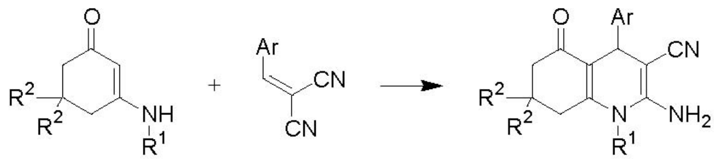
Introduction

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).[1,2] 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.**



1 **2**

It is conceivable that fused 1,4-dihydropyridines of type **2** with different substituents R^1 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]

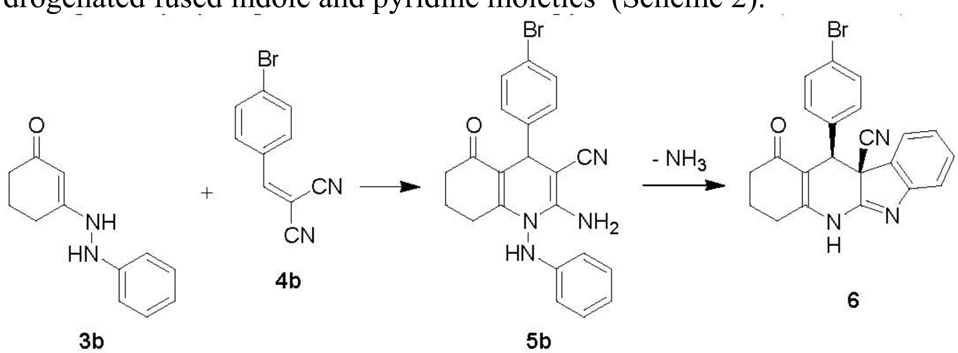


3 **4** **5**

3	R^1	R^2	5	Ar	4
a	Ph	Me	a	Ph	a
b	NHPh	H	b	4-BrC_6H_4	b
c	H	Me	c	Ph	a
d	*n*-C_5H_{11}	Me	d	4-ClC_6H_4	c
e	NMe_2	H	e	4-BrC_6H_4	b
f	CH_2CO_2Et	Me	f	3-$O_2NC_6H_4$	d
g	2-NCC_6H_4	Me	g	2,4-$Cl_2C_6H_3$	e

Scheme 1

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).

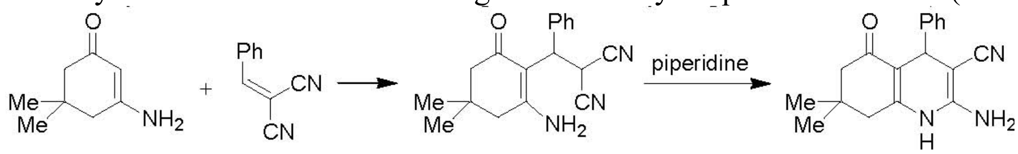


Scheme 2

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-arylidenemalononitriles 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

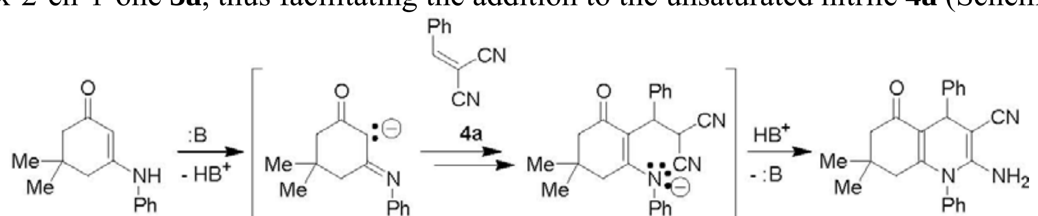
The N-unsubstituted 3-aminocyclohex-2-en-1-one **3c** readily reacted with 2-benzylidene-malononitrile **4a** upon short heating of a benzene solution in the presence of catalytic amounts of piperidine and afforded the N-unsubstituted hexahydroquinoline derivative **5c**. The reaction proceeded in two 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).



3c **4a** **7** **5c**

Scheme 3

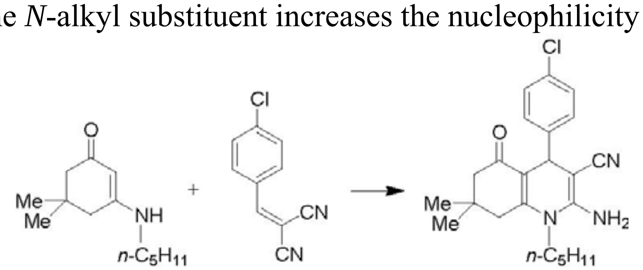
N-Aryl substituents decrease the nucleophilicity of enaminoketones **3** toward 2-arylidene-malononitriles **4**; a base catalyst was required to achieve the formation of the *N*-phenyl-substituted hexahydroquinoline **5a**.[3] Presumably, the base generates the anion of the 3-amino-cyclohex-2-en-1-one **3a**, thus facilitating the addition to the unsaturated nitrile **4a** (Scheme 4).



3a **5a**

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.

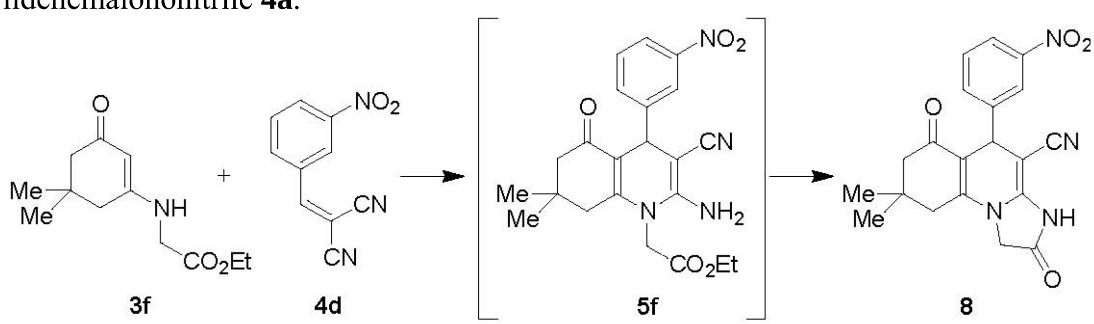


3d **4c** **5d**

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).[4] Also in this case a base was dispensable due to the increased nucleophilicity of the enehydrazinoketone. This is analogous to the earlier reported reaction[4] 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-arylidenemalononitriles **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 **5c** 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**.[3]

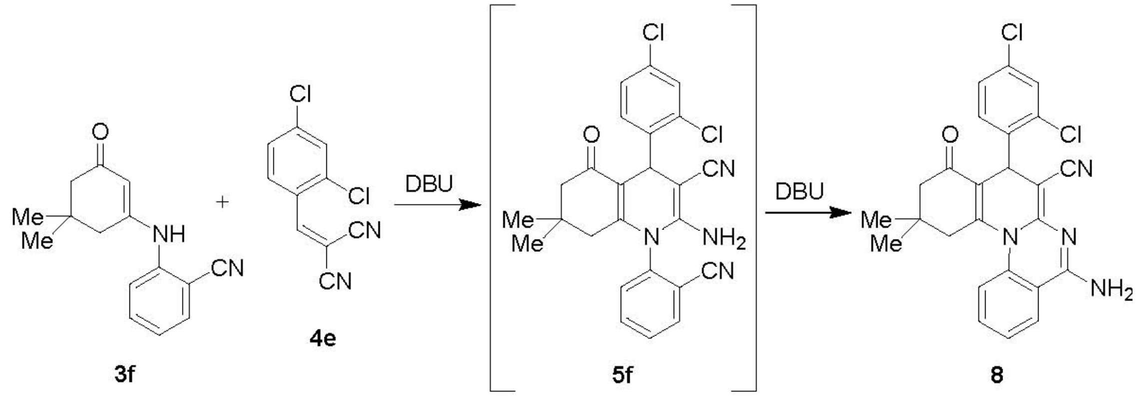


3f 4d 5f 8

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-dichlorbenzylidene)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).



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 $60F_{254}$, 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. ^{1}H and ^{13}C NMR spectra of DMSO-d_6 solutions were recorded with a Bruker AM-300 instrument.

The enaminoketones **3c**[6], **3d**[7], **3e**[4], **3g**[8] were prepared from the corresponding cyclohexa-1,3-diones and amines or hydrazines according to procedures described in the literature. 2-Arylidenemalononitriles **4a**,[9] **4b**,[10] **4c**,[11] **4d**,[12] **4e**[13] 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. ^{1}H NMR (300 MHz): δ 0.85 (3H, s, CH_3), 1.05 (3H, s, CH_3), 2.00 (1H, d, J = 18 Hz, CH_2), 2.20 (1H, d, J = 18 Hz, CH_2), 2.30–2.50 (2H, m, CH_2), 4.30 (1H, s, CH), 5.60 (2H, s, NH_2), 7.10–7.35 (5H, m, CH_{Ar}), 8.80 (1H, s, NH). Anal. Calcd for $C_{18}H_{19}N_3O$ (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. ^{1}H NMR (300 MHz): δ 0.85 (3H, s, CH_3), 1.00 (3H, s, CH_3), 2.00 (2H, s, CH_2), 2.30 (2H, s, CH_2), 4.50 (1H, d, J = 14 Hz, CH), 6.10 (1H, d, J = 14 Hz, CH), 7.20–7.50 (7H, m,

CH_{Ph}, NH_2). ^{13}C NMR (75 MHz): δ 25.85 (CH), 26.82 (CH_3), 28.22 (CH_3), 31.53 ($\underline{C}Me_2$), 41.91 (CH), 42.89 (CH_2), 50.59 (CH_2), 102.55 ($\underline{C}$=C–NH_2), 114.45 (CN), 114.69 (CN), 127.13 (CH_{Ph}), 127.95 (CH_{Ph}), 128.08 (CH_{Ph}), 139.21 (C_{Ph}), 163.30 (C–NH_2), 193.51 (CO). Anal. Calcd for $C_{18}H_{19}N_3O$ (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): δ 0.80 (3H, t, CH_3), 0.95 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.10–1.30 (4H, m, 2CH_2), 1.40–1.55 (2H, m, CH_2), 2.10–2.25 (2H, m, CH_2), 2.40 (1H, d, *J* = 18 Hz, CH_2), 2.65 (1H, d, *J* = 18 Hz, CH_2), 3.60 (1H, m, CH_2), 3.80 (1H, m, CH_2), 4.45 (1H, s, CH), 6.00 (2H, s, NH_2), 7.10 (2H, d, *J* = 8 Hz, CH_{Ar}), 7.30 (2H, d, *J* = 8 Hz, CH_{Ar}). Anal. Calcd for $C_{23}H_{28}ClN_3O$ (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 $MgSO_4$. 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): δ 1.00 (6H, s, 2CH_3), 1.20 (3H, t, *J* = 7 Hz, $C\underline{H}_3CH_2$), 1.95 (2H, s, CH_2), 2.20 (2H, s, CH_2), 3.85 (2H, d, *J* = 6 Hz, CH_2), 4.15 (2H, q, *J* = 7 Hz, $C\underline{H}_2CH_3$), 4.70 (1H, s, CH), 7.10 (1H, br t, *J* = 6 Hz, NH). Anal. Calcd for $C_{12}H_{19}NO_3$ (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-*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): δ 0.90 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.05 (1H, d, *J* = 18 Hz, CH_2), 2.20 (1H, d, *J* = 18 Hz, CH_2), 2.45 (1H, d, *J* = 18 Hz, CH_2), 2.60 (1H, d, *J* = 18 Hz, CH_2), 4.40 (2H, s, CH_2), 4.75 (1H, s, CH), 7.60 (1H, m, CH_{Ar}), 7.80 (1H, m, CH_{Ar}), 8.10 (2H, m, CH_{Ar}), 11.90 (1H, br s, NH). ^{13}C NMR (75 MHz): δ 26.21 (CH_3), 29.26 (CH_3), 31.73 ($\underline{C}Me_2$), 37.32 (CH), 38.19 (CH_2), 48.85 (CH_2), 49.43 (CH_2), 62.58 (3-C), 108.33 (5-C), 117.82 (CN), 121.56 (CH_{Ar}), 121.68 (CH_{Ar}), 129.88 (CH_{Ar}), 134.22 (CH_{Ar}), 147.62 ($C_{Ar}NO_2$), 147.73 (C_{Ar}), 149.06 (2-C), 149.17 (6-C), 170.15 (NCO), 193.79 (CO). Anal. Calcd for $C_{20}H_{18}N_4O_4$ (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-8*H*-quinolino-[1,2-*a*]quinazoline-7-carbonitrile (9). To a refluxing solution of **3g** (0.48 g, 2 mmol) and **4e** (0.45 g, 2 mmol) ethanol (7 mL) a few drops of DBU were added. The reaction mixture was refluxed for 5 h, than 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. ^{1}H NMR (300 MHz): δ 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. ^{1}H NMR (300 MHz): δ 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}). ^{13}C NMR (75 MHz): δ 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_{Ar}Br), 121.76 (CN), 128.92 (CH_{Ar}), 131.22 (CH_{Ar}), 146.15 (C_{Ar}), 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.

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