# Hydroamination of 2-Ethynyl-4,5,6,7-tetrahydroindoles: Toward 2-Substituted Amino Derivatives of Indole

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**Abstract:** Hydroamination of 1-phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-ones with secondary dialkylamines proceeds under mild conditions (room temperature, aqueous ethanol, 1 h) to afford the corresponding (2*E*)-3-dialkylamino-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-en-1-ones in 72–92% stereoselectivity and 64–88% yield. Under the same conditions, ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynoates react with dimethylamine and diethylamine in different ways; dimethylamine converts the ester function into an amide, giving the corresponding *N*,*N*-dimethyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynamides in 70–86% yield, whereas diethylamine adds to the triple bond to give the corresponding ethyl 3-(diethylamino)-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-enoates with ~100% stereoselectivity and up to 85% yield. The difference in the reactivity of the two amines can be rationalized in terms of steric hindrance.

**Key words:** indoles, alkynes, aminations, nucleophilic additions, amides

The addition of an N–H moiety to a C–C triple bond, a process known as hydroamination, offers an attractive route for the synthesis of substituted nitrogen-containing organic molecules without the formation of any side products (atom-economic methodology).[1] Hydroamination of an alkyne can provide either an enamine or an imine; these products can undergo further transformations,[2] the nature of which depends on the types of N–H and acetylenic species.

Enamines containing a carbonyl group in the β-position are important compounds in synthetic organic chemistry because of their use as 1,3-bielectrophilic or 1,3-binucleophilic synthons.[3,4] There are many reports on the functionalization of enaminones by means of various transformations at the nitrogen atom, the α-carbon atom, or the carbonyl group. These derivatives are used extensively in the preparation of a variety of heterocyclic systems, including some natural products and their analogues.[5]

The combination of an enaminone moiety and an indole nucleus in a single molecule can result in synergism between the properties of these important chemical structures, and could substantially expand the range of applications of enaminone-functionalized indoles as highly potent building blocks for organic and medicinal chemistry. These products, which combine the practically inexhaustible synthetic potentials of the indole nucleus, functional aminoethenes, and carbonyl compounds, show extraordinary flexibility as starting materials for the design of complex heterocyclic ensembles, including new alkaloids.

Recently, thanks to the discovery of transition-metal-free and solvent-free techniques for the ethynylation of the pyrrole nucleus with electrophilic haloalkynes on alumina[6] or other active surfaces,[7] 2-ethynylpyrroles, 2-ethynyl-4,5,6,7-tetrahydroindoles, and 3-ethynylindoles bearing electron-withdrawing substituents (acyl or alkoxycarbonyl groups) at the triple bond have become readily available. The new methodology has made 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-ones and 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynoates particularly accessible on a large-scale by using 4,5,6,7-tetrahydro-1*H*-indole[8] as the starting material. The hydroamination of these compounds with secondary amines can be considered as a shortcut to indole derivatives containing enaminone moieties, which, because of their ease of aromatization, may be suitable as intermediates for the synthesis of 2-functionalized indoles containing an amino function, e.g. α-analogues of tryptophan, tryptamine, serotonin, or melatonin.

In the present work, we have developed a convenient method for the synthesis of indole derivatives substituted with an enaminone moiety. The method is based on the nucleophilic addition of a secondary amine to the C–C triple bond of the 2-ethynyl-4,5,6,7-tetrahydro-1*H*-indoles **1a–c** and **2a–c**. Dimethylamine and diethylamine were chosen as secondary amines, and benzoyl and ethoxycarbonyl functions were selected as substituents for the ethynyl moiety.

The hydroamination of 1-phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynones **1a–c** with dimethylamine or diethylamine proceeded smoothly and stereoselectively at room temperature in ethanol for one hour (dimethylamine was used as a 24% aqueous solution). The adducts (64–88% yield) were *E*-isomers of the corresponding 3-(dialkylamino)-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1-phenylprop-2-en-1-ones **3a–c** and **4a–c**; these were obtained either exclusively (in the case of indole **1a**) or predominantly (in the case of indoles **1b** and **1c**) (Table 1).

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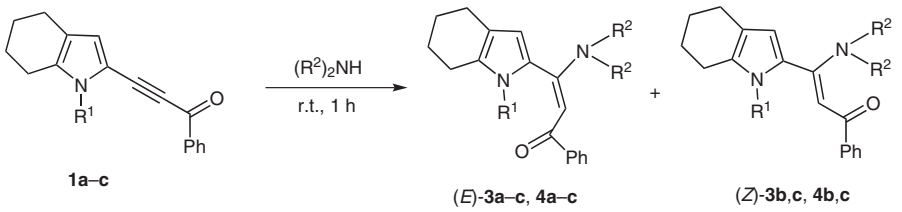
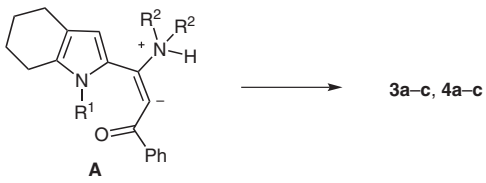
**Table 1** The Hydroamination of 1-Phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-ones **1a–c**




| Product | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **3a** | H | Me | 88 |
| **3b** | Me | Me | 87 |
| **3c** | Bn | Me | 80 |
| **4a** | H | Et | 64 |
| **4b** | Me | Et | 83 |
| **4c** | Bn | Et | 81 |

In the case of N-substituted indoles **1b** and **1c**, the stereoselectivity for the addition of diethylamine was always higher (92%) than that for dimethylamine (72–78%). The stereochemistry of the hydroamination of alkynes is known to be controlled by simultaneous intramolecular proton transfer to the emerging carbanion centre in the intermediate zwitterion **A**. This allows the *Z*-configuration of the carbanion to be fixed (Scheme 1).[9] In this case, however, the *E*-isomers were obtained not only as the kinetic, but also as the thermodynamic products, although minor amounts of the *Z*-isomer were obtained, probably as a result of the kinetically controlled reactions. Indeed, when a 78:22 mixture of the *E*- and *Z*-isomers of **3c** was boiled in benzene for one hour, only the *E*-isomer of **3c** remained in solution ($^1$H NMR), showing that the *Z*-isomer is readily and completely converted into the *E*-isomer.




**Scheme 1** The stereochemistry of the alkyne hydroamination reaction

The higher stability of the *E*-isomers of adducts **3a–c**, **4a–c** is surprising because they are sterically more strained than the corresponding *Z*-isomers. Whereas the NH-adducts **3a** and **4a** can be stabilized by intramolecular hydrogen bonding between the NH and the benzoyl function (Figure 1), this cannot take place for the N-substituted adducts **3b**, **3c**, **4b**, and **4c**. It is therefore likely that most of the stabilization of the *E*-isomers is provided by the stronger conjugation between the dialkylamino and benzoyl substituents when these have a *trans*-orientation, in agreement with reports in the literature.[9]

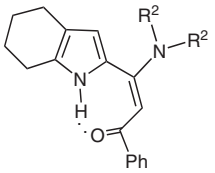
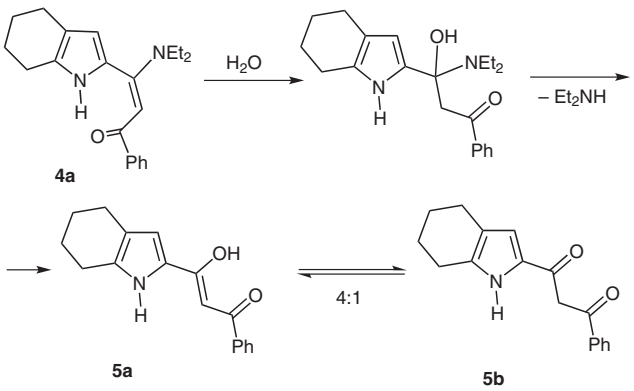


**Figure 1** Intramolecular hydrogen bonding in compounds **3a** and **4a**

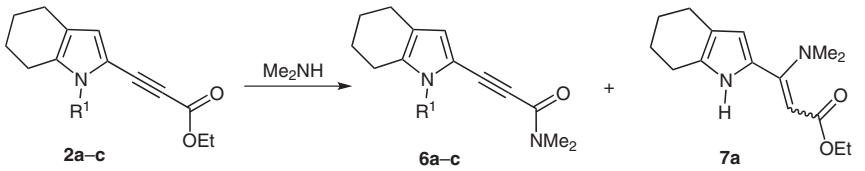
The hydroamination of indole **1a** with diethylamine (1:1 aqueous ethanol, triethylamine, 50 °C, 1 h) was accompanied by formation of minor amounts of enol **5a** and its keto tautomer **5b** (4:1 ratio; yield 6%), as a result of hydrolysis of adduct **4a** (Scheme 2). This shows that water does not add across the triple bond of indole **1a**, but that the adduct **4a** is almost completely converted into the enol–ketone equilibrium mixture of **5a** and **5b** (4:1).




**Scheme 2** The formation of the enol–ketone mixture of **5a** and **5b**

In contrast to the hydroamination of indoles **1a–c** by dimethylamine, this amine failed to add to the triple bond of ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynoates **2a–c**. Surprisingly, under analogous conditions (aqueous 24% dimethylamine, room temperature, 1 h), the esters

**Table 2** Reactions of Ethyl 3-(4,5,6,7-Tetrahydro-1*H*-indol-2-yl)prop-2-ynoates **2a–c** with Dimethylamine




| Pyrrole | $R^1$ | Yield (%) |
|---|---|---|
| **6a** | H | 70[a] |
| **6b** | Me | 77 |
| **6c** | Bn | 86 |

[a] Minor amounts of the expected product **7a** were also obtained (NMR).

**2a–c** were readily converted into the corresponding *N*,*N*-dimethyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynamides **6a–c** in 70–86% yields, the triple bond remaining intact despite the presence of a large excess of dimethylamine (Table 2).

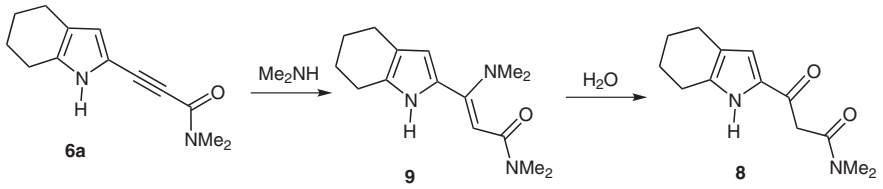
Minor amounts (6–8%) of the expected adduct (**7a**) were discernible ($^1$H NMR) only in the case of the reaction of indole **2a**. When the reaction of indole **2a** with dimethylamine was performed at a higher temperature (50 °C, 1 h), *N*,*N*-dimethyl-3-oxo-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propanamide (**8**) was obtained as the major product, together with the propynamide **6a**, in a ratio of 4:1.

Ketone **8** was also formed selectively in 64% yield by heating propynamide **6a** in aqueous dimethylamine at 50 °C for one hour, probably as a result of hydrolysis of adduct **9** (Scheme 3). The straightforward hydrolysis of amide **6a** with water in the presence of triethylamine (50 °C, 1 h) did not occur, and amide **6a** was recovered.

Propynamides are generally considered to be key intermediates in heterocyclic chemistry,[10] so that the synthesized *N*,*N*-dimethyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propynamides **6a–c** are likely to be useful building blocks, particularly for the preparation of previously inaccessible functional indole derivatives.

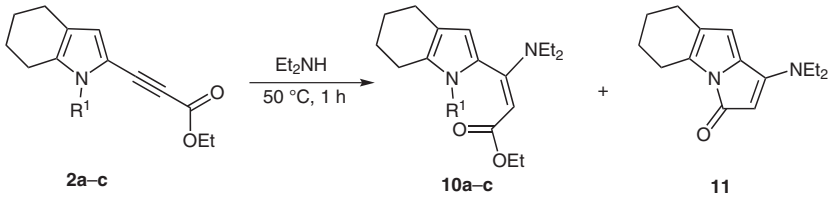
Unlike dimethylamine, diethylamine reacted with propynoates **2a–c** (aqueous ethanol, 50 °C, 1 h) by hydroamination to give the *E*-isomers of adducts **10a–c** stereospecifically in up to 85% yield (Table 3).

The reaction of propynoate **2a** with diethylamine was accompanied by partial intramolecular cyclization of the primary adduct **10a** to form the pyrroloindole **11**; the ratio of **10a** to **11** was 1:1. Attempts to separate this mixture by column chromatography on alumina resulted in the isolation of pyrroloindole **11** exclusively as a result of the complete cyclization of adduct **10a**.




**Scheme 3** Synthesis of *N*,*N*-dimethyl-3-oxo-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propanamide (**8**)

**Table 3** Reactions of Ethyl 3-(4,5,6,7-Tetrahydro-1*H*-indol-2-yl)prop-2-ynoates **2a–c** with Diethylamine




| Pyrrole | $R^1$ | Yield (%) |
|---|---|---|
| **10a** | H | 37 |
| **11** | | 34 |
| **10b** | Me | 85 |
| **10c** | Bn | 84 |

Thus, dimethylamine and diethylamine reacted with indoles **2a–c** in different ways. With dimethylamine, the propynamides **6a–c** were formed, whereas amidation did not occur in the case of diethylamine. When aqueous diethylamine of the same concentration as dimethylamine (24%) was used, the indole **2a** also failed to give the propynamide either at room temperature or on heating (50 °C, 1 h). In the latter case, as with neat diethylamine, the adducts **10a–c** were formed exclusively.

This unexpected and pronounced difference in the reactivity of dimethylamine and diethylamine towards propynoates **2a–c** can probably be attributed to differences in the steric characteristics of these two amines, because their basicities and their nucleophilicities are similar.[11] There is at least one other reported case in which the rate of reaction of diethylamine was found to be two orders of magnitude slower than that of dimethylamine as a result of their different steric requirements.[12]

To summarize, a new method has been developed for the synthesis of 2-substituted amino derivatives of 4,5,6,7-tetrahydro-1*H*-indoles. The method is based on the hydroamination of available 2-ethynyl-4,5,6,7-tetrahydro-1*H*-indoles bearing electron-withdrawing substituents at the triple bond. The addition of a secondary dialkylamine across the triple bond of a 1-phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-one gives predominantly the corresponding *E*-adduct in 72–92% stereoselectivity and 64–88% yield. Dimethylamine and diethylamine showed different behaviors in their reactions with ethyl 3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynoates. Whereas the former chemoselectively converted the ester function into an amide function, the latter added chemo-, regio-, and stereoselectively to the triple bond. In the case of the N–H derivative of 4,5,6,7-tetrahydro-1*H*-indole, partial intramolecular cyclization occurred to give pyrroloindole in addition to the corresponding adduct. This new methodology opens a route to previously inaccessible 2-substituted amino derivates of indole and to analogues of tryptophan, tryptamine, serotonin, melatonin, and other important physiologically significant indole compounds.

IR spectra were recorded on a Bruker Vertex 70 spectrometer (400–4000 $cm^{-1}$, KBr pellets). The $^1H$ (400.13 MHz) and $^{13}C$ NMR (101.6 MHz) spectra were recorded on Bruker DPX-400 instrument. In all cases, the $^1H$ and $^{13}C$ resonances were assigned by concerted application of COSY and NOESY $^1H$–$^1H$ 2D homonuclear experiments and by HSQC and HMBC $^1H$–$^{13}C$ 2D heteronuclear experiments, respectively. 1-Phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-ones **1a–c** and ethyl 3-(4,5,6,7-tetrahydro-1*H*-indoles-2-yl)prop-2-ynoates **2a–c** were prepared from the corresponding pyrroles and 3-bromo-1-phenylprop-2-yn-1-one or ethyl 3-bromoprop-2-ynoate, respectively, according to the literature methods.[6,7]

### Hydroamination of 1-Phenyl-3-(4,5,6,7-tetrahydro-1*H*-indoles-2-yl)prop-2-yn-1-ones 1a–c with Dimethylamine; General Procedure

A 24% aq soln of $Me_2NH$ (5 mL) was added to a soln of indole **1a–c** (1 mmol) in EtOH (2 mL), and the mixture was stirred at r.t. for 1 h. The mixture was then diluted with $H_2O$ (1:2) and extracted with $Et_2O$ (5 × 3 mL). The extracts were washed with $H_2O$ (3 × 3 mL) and dried ($K_2CO_3$). The residue after removal of $Et_2O$ was purified by flash chromatography ($Al_2O_3$, hexane then $Et_2O$) to give corresponding adducts **3a–c**.

### (2*E*)-3-(Dimethylamino)-1-phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-en-1-one (3a)

Light yellow crystals; yield: 88%; mp 144–145 °C.

IR (KBr): 3435, 3030, 2921, 2850, 2804, 1656, 1618, 1590, 1559, 1500, 1484, 1432, 1383, 1276, 1238, 1218, 1171, 1153, 1141, 1051, 1024, 991, 967, 922, 832, 758, 746, 699, 621 $cm^{-1}$.

$^1H$ NMR (400.13 MHz, $CDCl_3$): δ = 1.80 (m, 4 H, $CH_2$-5,6), 2.57 (m, 2 H, $CH_2$-4), 2.70 (m, 2 H, $CH_2$-7), 3.14 (s, 6 H, $NMe_2$), 5.67 (s, 1 H, HC=), 6.31 (s, 1 H, H-3), 7.36 (m, 3 H, $H_{m,p}$), 7.85 (m, 2 H, $H_o$), 10.00 (br s, 1 H, NH).

$^{13}C$ NMR (101.6 MHz, $CDCl_3$): δ = 23.0, 23.3, 23.5, 23.7 ($CH_2$-4,5,6,7), 43.6 ($NMe_2$), 93.1 (HC=), 114.4 (C-3), 119.9 (C-4), 124.1 (C-2), 127.6 ($C_o$), 128.0 ($C_m$), 130.2 ($C_p$), 132.1 (C-5), 142.6 ($C_i$), 158.3 (=CN), 185.6 (CO).

Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: 77.28; H, 7.39; N, 9.73.

### (2*E*/*Z*)-3-(Dimethylamino)-3-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1-phenylprop-2-en-1-one (3b)

Yellow oil; Yield: 87%; *E*/*Z* = 72:28.

IR (KBr): 3437, 3055, 2924, 2852, 1631, 1596, 1574, 1514, 1461, 1423, 1384, 1296, 1219, 1195, 1168, 1132, 1046, 1016, 936, 918, 764, 699 $cm^{-1}$.

$^1H$ NMR (400.13 MHz, $CDCl_3$): δ (*E*-isomer) = 1.70 (m, 4 H, $CH_2$-5,6), 2.48 (m, 2 H, $CH_2$-4), 2.52 (m, 2 H, $CH_2$-7), 3.00 (s, 6 H, $NMe_2$), 3.30 (s, 3 H, NMe), 5.83 (s, 1 H, HC=), 5.85 (s, 1 H, H-3), 7.31 (m, 2 H, $H_m$), 7.34 (m, 1 H, $H_p$), 7.72 (m, 2 H, $H_o$).

$^1H$ NMR (400.13 MHz, $CDCl_3$): δ (*Z*-isomer) = 1.80 (m, 4 H, $CH_2$-5,6), 2.48 (m, 2 H, $CH_2$-4), 2.53 (m, 2 H, $CH_2$-7), 3.10 (s, 6 H, $NMe_2$), 3.44 (s, 3 H, NMe), 5.68 (s, 1 H, HC=), 6.18 (s, 1 H, H-3), 7.38 (m, 3 H, $H_{m,p}$), 7.92 (m, 2 H, $H_o$).

$^{13}C$ NMR (101.6 MHz, $CDCl_3$): δ (*E*-isomer) = 22.2, 23.0, 23.2, 23.5 ($CH_2$-4,5,6,7), 30.0 (NMe), 41.0 ($NMe_2$), 97.4 (HC=), 110.3 (C-3), 117.3 (C-4), 125.1 (C-2), 127.5 ($C_m$), 127.6 ($C_o$), 130.1 ($C_p$), 131.1 (C-5), 142.4 ($C_i$), 156.4 (=CN), 189.0 (CO).

$^{13}C$ NMR (101.6 MHz, $CDCl_3$): δ (*Z*-isomer) = 22.2, 23.0, 23.2, 23.5 ($CH_2$-4,5,6,7), 31.2 (NMe), 43.5 ($NMe_2$), 96.5 (HC=), 113.6 (C-3), 118.2 (C-4), 127.9 ($C_o$), 128.0 ($C_m$), 128.7 (C-2), 130.4 ($C_p$), 133.2 (C-5), 142.3 ($C_i$), 155.9 (=CN), 184.1 (CO).

Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 77.58; H, 7.95; N, 9.24.

### (2*E*/*Z*)-3-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-(dimethylamino)-1-phenylprop-2-en-1-one (3c)

Yellow oil; Yield: 80%; *E*/*Z* = 78:22.

IR (KBr): 3435, 3058, 3027, 2923, 2850, 1630, 1575, 1513, 1426, 1390, 1294, 1218, 1133, 1050, 1022, 918, 767, 696 $cm^{-1}$.

$^1H$ NMR (400.13 MHz, $CDCl_3$): δ (*E*-isomer) = 1.79 (m, 4 H, $CH_2$-5,6), 2.48 (m, 4 H, $CH_2$-4,7), 2.73 (br s, 6 H, $NMe_2$), 4.80 (d, *J* = 16.0 Hz, 1 H, $CH_2$), 4.94 (d, *J* = 16.0 Hz, 1 H, $CH_2$), 5.78 (s, 1 H, HC=), 5.91 (s, 1 H, H-3), 6.98 (m, 2 H, $H_o$ $CH_2Ph$), 7.19–7.33 (m, 6 H, $H_{m,p}$ $CH_2Ph$, COPh), 7.81 (m, 2 H, $H_o$ COPh).

$^1H$ NMR (400.13 MHz, $CDCl_3$): δ (*Z*-isomer) = 1.79 (m, 4 H, $CH_2$-5,6), 2.48 (m, 4 H, $CH_2$-4,7), 2.98 (s, 6 H, $NMe_2$), 5.06 (br s, 2 H, $CH_2$), 5.58 (s, 1 H, HC=), 6.20 (s, 1 H, H-3), 6.84 (m, 2 H, $H_o$ $CH_2Ph$), 7.19–7.33 (m, 6 H, $H_{m,p}$ $CH_2Ph$, COPh), 7.70 (m, 2 H, $H_o$ COPh).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ (*E*-isomer) = 22.4, 23.1, 23.2, 23.6 ($CH_2$-4,5,6,7), 29.7 ($NMe_2$), 46.8 ($CH_2$), 95.6 (HC=), 109.9 (C-3), 117.6 (C-4), 124.7 (C-2), 127.0 ($C_p$ $CH_2Ph$), 127.1 ($C_m$ $CH_2Ph$), 127.5 ($C_o$ $CH_2Ph$), 127.9 ($C_m$ COPh), 128.3 ($C_o$ COPh), 130.2 ($C_p$ COPh), 130.8 (C-5), 139.3 ($C_i$ $CH_2Ph$), 142.3 ($C_i$ COPh), 156.6 (=CN), 187.5 (CO).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ (*Z*-isomer) = 22.4, 23.1, 23.2, 23.6 ($CH_2$-4,5,6,7), 30.6 ($NMe_2$), 47.2 ($CH_2$), 95.8 (HC=), 113.8 (C-3), 118.3 (C-4), 126.0 (C-2), 127.1 ($C_p$ $CH_2Ph$), 127.4 ($C_m$, $CH_2Ph$), 127.8 ($C_o$ $CH_2Ph$), 128.4 ($C_m$ COPh), 128.5 ($C_o$ COPh), 130.5 ($C_p$ COPh), 133.1 (C-5), 138.3 ($C_i$ $CH_2Ph$), 141.4 ($C_i$ COPh), 155.7 (=CN), 183.8 (CO).

Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.29. Found: C, 80.89; H, 7.15; N, 7.13.

**Hydroamination of 1-Phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-yn-1-one (1a) with Diethylamine; Typical Procedure**

$Et_2NH$ (1 mL) was added to a soln of indole **1a** (0.200 g, 0.8 mmol) in EtOH (2 mL), and the mixture was stirred at r.t. for 1 h. The mixture was then diluted with $H_2O$ (1:3) and extracted with $Et_2O$ (5 × 3 mL). The extracts were washed with $H_2O$ (3 × 3 mL) and dried ($K_2CO_3$). The residue (0.194 g) after removal of $Et_2O$ was washed with cold $Et_2O$ (3 mL) to give enol **5a** together with its tautomer **5b** in a 4:1 ratio; yield: 0.013 g (6%). Fractionated of the $Et_2O$ soln by column chromatography [$Al_2O_3$, hexane–$Et_2O$ (1:1)] gave the adduct **4a**; yield: 0.166 g (64%).

Adducts **4b** and **4c** were obtained analogously.

**(2*E*)-3-(Diethylamino)-1-phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-en-1-one (4a)**

Yellow crystals; yield: 64%; mp 128–129 °C.

IR (KBr): 3207, 3004, 2927, 2850, 2838, 1599, 1582, 1541, 1496, 1456, 1436, 1356, 1340, 1321, 1308, 1293, 1263, 1250, 1150, 1140, 1093, 1067, 998, 817, 787, 772, 739, 702, 639, 515 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.0 Hz, 6 H, Me), 1.75 (m, 4 H, $CH_2$-5,6), 2.50 (m, 2 H, $CH_2$-4), 2.61 (m, 2 H, $CH_2$-7), 3.52 (q, *J* = 7.0 Hz, 4 H, $NCH_2$), 5.79 (s, 1 H, HC=), 6.25 (s, 1 H, H-3), 7.34 (m, 3 H, $H_{m,p}$), 7.79 (m, 2 H, $H_o$), 10.65 (br s, 1 H, NH).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 13.0 (2 Me), 23.0, 23.1, 23.2, 23.7 ($CH_2$-4,5,6,7), 45.8 (2 $NCH_2$), 95.3 (HC=), 112.6 (C-3), 119.4 (C-4), 124.6 (C-2), 127.5 ($C_o$), 127.9 ($C_m$), 130.1 ($C_p$), 131.6 (C-5), 142.7 ($C_i$), 157.3 (=CN), 186.4 (CO).

Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 77.94; H, 8.25; N, 8.47.

**(2*Z*)-3-Hydroxy-1-phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-en-1-one (5a) and 1-Phenyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propane-1,3-dione (5b)**

Yellow crystals; yield: 6%; mp 200–202 °C.

IR (KBr): 3414, 3368, 3276, 3063, 3030, 2925, 2851, 1730, 1626, 1598, 1573, 1529, 1507, 1473, 1447, 1447, 1389, 1368, 1389, 1364, 1327, 1271, 1225, 1190, 1145, 1068, 972, 833, 815, 802, 771, 691, 614, 561 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ (enol **5a**) = 1.78 (m, 4 H, $CH_2$-5,6), 2.52 (m, 2 H, $CH_2$-4), 2.63 (m, 2 H, $CH_2$-7), 6.47 (s, 1 H, HC=), 6.73 (s, 1 H, H-3), 7.43 (m, 3 H, $H_{m,p}$), 7.87 (m, 2 H, $H_o$), 9.17 (br s, 1 H, NH), 16.04 (s, 1 H, OH).

$^1$H NMR (400.13 MHz, $CDCl_3$): δ (diketone **5b**) = 1.78 (m, 4 H, $CH_2$-5,6), 2.52 (m, 2 H, $CH_2$-4), 2.58 (m, 2 H, $CH_2$-7), 4.34 (s, 2 H, $CH_2$), 6.77 (s, 1 H, H-3), 7.52 (m, 3 H, $H_{m,p}$), 8.03 (m, 2 H, $H_o$), 9.04 (br s, 1 H, NH).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ (enol **5a**) = 22.8, 22.9, 23.1, 23.5 ($CH_2$-4,5,6,7), 92.9 (HC=), 114.5 (C-3), 121.1 (C-4), 126.4 (C-2), 128.6 ($C_m$), 128.9 ($C_o$), 131.4 ($C_p$), 134.7 (C-5), 136.3 ($C_i$), 175.2 (CO), 181.5 (COH).

**(2*E*/*Z*)-3-(Diethylamino)-3-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1-phenylprop-2-en-1-one (4b)**

Light yellow crystals; yield: 83%; *E*/*Z* = 92:8; mp 94–96 °C.

IR (KBr): 3449, 3057, 2976, 2926, 2845, 1614, 1596, 1575, 1532, 1508, 1479, 1433, 1354, 1276, 1215, 1198, 1155, 1072, 1052, 1026, 992, 897, 812, 777, 705, 656 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ (*E*-isomer) = 1.18 (br s, 6 H, Me), 1.72 (m, 4 H, $CH_2$-5,6), 2.45 (m, 4 H, $CH_2$-4,7), 3.24 (s, 3 H, NMe), 3.34 (br m, 4 H, $NCH_2$), 5.82 (s, 1 H, HC=), 5.92 (s, 1 H, H-3), 7.28 (m, 3 H, $H_{m,p}$), 7.68 (m, 2 H, $H_o$).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ (*E*-isomer) = 13.2 (2 Me), 21.9, 23.0, 23.1, 23.5 ($CH_2$-4,5,6,7), 29.9 (NMe), 46.2 (2 $NCH_2$), 96.6 (HC=), 108.3 (C-3), 116.9 (C-4), 124.9 (C-2), 127.2 ($C_m$), 127.5 ($C_o$), 129.7 ($C_p$), 130.2 (C-5), 142.4 ($C_i$), 155.0 (=CN), 188.6 (CO).

Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.13; H, 8.19; N, 8.01.

**(2*E*/*Z*)-3-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-(diethylamino)-1-phenylprop-2-en-1-one (4c)**

Light yellow solid; yield: 81%; *E*/*Z* = 92:8; mp 106–108 °C.

IR (KBr): 3436, 3059, 3030, 2964, 2927, 2849, 1626, 1572, 1524, 1479, 1457, 1434, 1378, 1355, 1345, 1218, 1197, 1158, 1074, 1055, 999, 898, 782, 730, 698 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ (*E*-isomer) = 0.99 (br s, 6 H, Me), 1.70 (m, 4 H, $CH_2$-5,6), 2.45 (m, 2 H, $CH_2$-4), 2.54 (m, 2 H, $CH_2$-7), 3.24 (br m, 4 H, $NCH_2$), 4.78 (d, *J* = 16.0 Hz, 1 H, $CH_2$), 4.90 (d, *J* = 16.0 Hz, 1 H, $CH_2$), 5.86 (s, 1 H, HC=), 5.91 (s, 1 H, H-3), 6.98 (m, 2 H, $H_o$ $CH_2Ph$), 7.20 (m, 3 H, $H_{m,p}$ $CH_2Ph$), 7.32 (m, 3 H, $H_{m,p}$ COPh), 7.78 (m, 2 H, $H_o$ COPh).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ (*E*-isomer) = 14.1 (2 Me), 22.6, 23.2, 23.4, 23.7 ($CH_2$-4,5,6,7), 41.1 (2 $NCH_2$), 46.9 ($CH_2$), 94.6 (HC=), 109.2 (C-3), 117.3 (C-4), 124.8 (C-2), 127.0 ($C_p$ $CH_2Ph$), 127.2 ($C_m$ $CH_2Ph$), 127.4 ($C_o$ $CH_2Ph$), 127.9 ($C_m$ COPh), 128.4 ($C_o$ COPh), 130.1 ($C_p$ COPh), 130.9 (C-5), 139.4 ($C_i$ $CH_2Ph$), 142.7 ($C_i$ COPh), 155.5 (=CN), 187.6 (CO).

Anal. Calcd for $C_{28}H_{32}N_2O$: C, 81.51; H, 7.82; N, 6.79. Found: C, 81.13; H, 7.52; N, 6.57.

***N*,*N*-Dimethyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynamide (6a); Typical Procedure**

A 24% aq soln of $Me_2NH$ (5 mL) was added to a soln of indole **2a** (0.217 g, 1 mmol) in EtOH (2 mL), and the mixture was stirred at r.t. for 1 h. The mixture was then diluted with $H_2O$ (1:2) and filtered to give yellow crystals: yield: 0.152 g (70%); mp 220–221 °C [aq acetone (1:1)]. Minor amounts of the expected product **7a** were detected by $^1$H NMR.

IR (KBr): 3225, 3157, 3072, 2936, 2853, 2183, 1616, 1583, 1434, 1397, 1359, 1302, 1264, 1182, 1160, 1114, 827, 814, 719 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.74 (m, 4 H, $CH_2$-5,6), 2.45 (m, 2 H, $CH_2$-4), 2.55 (m, 2 H, $CH_2$-7), 2.98 (s, 3 H, $NMe_2$), 3.20 (s, 3 H, $NMe_2$), 6.38 (s, 1 H, H-3), 8.39 (br s, 1 H, NH).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 22.7, 23.0, 23.1, 23.5 ($CH_2$-4,5,6,7), 34.1 ($NMe_2$), 38.3 ($NMe_2$), 84.9 (C≡), 86.2 (≡C), 108.0 (C-2), 117.3 (C-3), 118.9 (C-4), 132.5 (C-5), 155.6 (CO).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.86; H, 7.25; N, 12.59.

**Ethyl 3-(Dimethylamino)-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylate (7a)**

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.1 Hz, 3 H, Me), 1.75 (m, 4 H, $CH_2$-5,6), 2.48 (m, 2 H, $CH_2$-4), 2.61 (m, 2 H, $CH_2$-7), 2.90 (s, 6 H, $NMe_2$), 4.03 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 4.71 (s, 1 H, HC=), 6.17 (s, 1 H, H-3), 9.80 (br s, 1 H, NH).

The *N*,*N*-dimethyl-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynamides **6b** and **6c** were prepared similarly.

***N*,*N*-Dimethyl-3-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)prop-2-ynamide (6b)**

Yellow crystals; yield: 77%; mp 107–108 °C.

IR (KBr): 3437, 2934, 2849, 2185, 1617, 1503, 1465, 1388, 1264, 1202, 1116, 1054, 837, 816, 722, 545 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.70 (m, 2 H, $CH_2$-5), 1.80 (m, 2 H, $CH_2$-6), 2.45 (m, 2 H, $CH_2$-4), 2.50 (m, 2 H, $CH_2$-7), 2.99 (s, 3 H, $NMe_2$), 3.22 (s, 3 H, $NMe_2$), 3.51 (s, 3 H, NMe), 6.39 (s, 1 H, H-3).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 22.4, 22.8, 22.9, 23.3 ($CH_2$-4,5,6,7), 31.1 (NMe), 34.1 ($NMe_2$), 38.2 ($NMe_2$), 84.9 (C≡), 89.9 (≡C), 111.0 (C-2), 116.6 (C-3), 118.6 (C-4), 133.6 (C-5), 155.4 (CO).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.95; H, 7.62; N, 12.43.

**3-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-*N*,*N*-dimethylprop-2-ynamide (6c)**

Greyish crystals; yield: 86%; mp 94–95 °C.

IR (KBr): 3456, 3064, 2930, 2854, 2182, 1622, 1495, 1436, 1389, 1377, 1361, 1268, 1237, 1148, 824, 805, 730, 697 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.68 (m, 2 H, $CH_2$-6), 1.73 (m, 2 H, $CH_2$-5), 2.49 (m, 2 H, $CH_2$-4), 2.59 (m, 2 H, $CH_2$-7), 2.93 (s, 3 H, $NMe_2$), 3.02 (s, 3 H, $NMe_2$), 5.11 (s, 2 H, $CH_2$), 6.49 (s, 1 H, H-3), 7.01 (m, 2 H, $H_o$), 7.26 (m, 3 H, $H_{m,p}$).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 22.6, 22.9, 23.0, 23.3 ($CH_2$-4,5,6,7), 34.1 ($NMe_2$), 38.1 ($NMe_2$), 48.2 ($CH_2$), 84.9 (C≡), 87.9 (≡C), 111.3 (C-2), 117.4 (C-3), 119.3 (C-4), 126.5 ($C_o$), 127.4 ($C_p$), 128.8 ($C_m$), 133.6 (C-5), 137.7 ($C_i$), 155.3 (CO).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.21; H, 7.02; N, 8.89.

***N*,*N*-Dimethyl-3-oxo-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)propanamide (8)**

A 24% aq soln of $Me_2NH$ (5 mL) was added to a soln of propynamide **6a** (0.216 g, 1 mmol) in EtOH (2 mL), and the mixture was stirred at 50 °C for 1.5 h. The mixture was diluted with $H_2O$ (1:3) and extracted with $Et_2O$ (5 × 3 mL). The extracts were washed with $H_2O$ (3 × 3 mL) and dried ($K_2CO_3$). The residue after removal of $Et_2O$ was washed with cold $Et_2O$ and dried to give grey crystals; yield: 0.150 g (64%); mp 148–149 °C.

IR (KBr): 3429, 3263, 2929, 2857, 1649, 1621, 1516, 1499, 1463, 1398, 1364, 1334, 1261, 1228, 1182, 1144, 1124, 1053, 956, 856, 614 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.75 (m, 4 H, $CH_2$-5,6), 2.49 (m, 2 H, $CH_2$-4), 2.59 (m, 2 H, $CH_2$-7), 2.94 (s, 3 H, $NMe_2$), 3.01 (s, 3 H, $NMe_2$), 3.80 (s, 2 H, $CH_2$), 6.80 (s, 1 H, H-3), 9.13 (br s, 1 H, NH).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 22.7, 22.9, 23.1, 23.5 ($CH_2$-4,5,6,7), 35.7 ($NMe_2$), 38.3 ($NMe_2$), 45.7 ($CH_2$), 117.4 (C-3), 129.0 (C-4), 129.7 (C-2), 137.5 (C-5), 167.6 (NCO), 181.9 (CO).

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.28; H, 7.56; N, 11.59.

**Reaction of Ethyl 3-(4,5,6,7-Tetrahydro-1*H*-indol-2-yl)prop-2-ynoates 2a–c with Diethylamine; General Procedure**

$Et_2NH$ (1 mL) was added to a soln of indole **2a–c** (1 mmol) in EtOH (2 mL), and the mixture was stirred at r.t. for 1 h. The mixture was then diluted with $H_2O$ (1:3) and extracted with $Et_2O$ (5 × 3 mL). The extracts were washed with $H_2O$ (3 × 3 mL) and dried ($K_2CO_3$). The residue after removing $Et_2O$ was fractionated by column chromatography [$Al_2O_3$, hexane–$Et_2O$ (1:1)] to afford the corresponding adduct **10b**, **10c,** or **11**.

**Ethyl (2*E*)-3-(Diethylamino)-3-(4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylate (10a)**

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.07 (m, 6 H, Me), 1.23 (t, *J* = 7.1 Hz, 3 H, Me), 1.75 (m, 4 H, $CH_2$-5,6), 2.48 (m, 2 H, $CH_2$-4), 2.61 (m, 2 H, $CH_2$-7), 3.24 (q, *J* = 7.0 Hz, 4 H, $NCH_2$), 4.00 (q, *J* = 7.1, 2 H, $OCH_2$), 4.78 (s, 1 H, HC=), 6.05 (s, 1 H, H-3), 8.90 (br s, 1 H, NH).

**Ethyl (2*E*)-3-(Diethylamino)-3-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)acrylate (10b)**

Light brown oil; yield: 85%.

IR (KBr): 3494, 3095, 2975, 2930, 2851, 2184, 1699, 1666, 1590, 1564, 1506, 1445, 1362, 1273, 1253, 1191, 1171, 1136, 1083, 1049, 1008, 927, 799, 713 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.04 (m, 9 H, Me), 1.66 (m, 2 H, $CH_2$-6), 1.77 (m, 2 H, $CH_2$-5), 2.47 (m, 4 H, $CH_2$-4,7), 3.13 (m, 4 H, $NCH_2$), 3.19 (s, 3 H, NMe), 3.90 (m, 2 H, $OCH_2$), 4.83 (s, 1 H, HC=), 5.72 (s, 1 H, H-3).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 14.6 (3 Me), 22.1, 23.2, 23.4, 23.8 ($CH_2$-4,5,6,7), 29.9 (NMe), 43.7 (2 $NCH_2$), 58.4 ($OCH_2$), 87.9 (HC=), 106.7 (C-2), 116.7 (C-3), 125.0 (C-4), 128.8 (C-5), 154.0 (=CN), 168.0 (CO).

Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 70.75; H, 9.00; N, 8.95.

**Ethyl (2*E*)-3-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3-(diethylamino)acrylate (10c)**

Light yellow oil; yield: 84%.

IR (KBr): 3481, 3063, 3030, 2975, 2931, 2852, 2242, 2183, 1954, 1695, 1662, 1588, 1557, 1505, 1455, 1419, 1380, 1291, 1273, 1254, 1197, 1189, 1167, 1132, 1116, 1088, 1049, 1049, 925, 799, 698 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 0.91 (m, 6 H, Me), 1.12 (t, *J* = 7.1 Hz, 3 H, Me), 1.78 (m, 4 H, $CH_2$-5,6), 2.49 (m, 2 H, $CH_2$-4), 2.56 (m, 2 H, $CH_2$-7), 2.99 (br s, 4 H, $NCH_2$), 3.95 (q, *J* = 7.1 Hz, 2 H, $OCH_2$), 4.82 (s, 1 H, HC=), 4.80 (d, *J* = 7.6 Hz, 1 H, $CH_2Ph$), 4.85 (d, *J* = 7.6 Hz, 1 H, $CH_2Ph$), 5.84 (s, 1 H, H-3), 7.01 (m, 2 H, $H_o$), 7.19 (m, 3 H, $H_{m,p}$).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 14.3 (3 Me), 22.3, 22.9, 23.2, 23.5 ($CH_2$-4,5,6,7), 43.1 (2 $NCH_2$), 46.6 ($CH_2$), 58.0 ($OCH_2$), 86.5 (HC=), 107.7 (C-2), 116.7 (C-3), 124.5 (C-4), 126.6 ($C_p$), 126.9 ($C_o$), 128.0 ($C_m$), 128.9 (C-5), 138.6 ($C_i$), 153.8 (=CN), 167.6 (CO).

Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 75.52; H, 8.39; N, 7.48.

**1-(Diethylamino)-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indol-3-one (11)**

Orange crystals; yield: 34%; mp 100–101 °C.

IR (KBr): 3439, 3105, 2987, 2969, 2930, 2867, 2847, 1694, 1598, 1505, 1468, 1451, 1427, 1395, 1378, 1362, 1348, 1325, 1303, 1257, 1210, 1154, 1111, 1077, 991, 958, 802, 779, 750, 710, 648, 620, 607 cm$^{-1}$.

$^1$H NMR (400.13 MHz, $CDCl_3$): δ = 1.23 (t, J = 6.6 Hz, 6 H, Me), 1.72 (m, 4 H, $CH_2$-5,6), 2.39 (m, 2 H, $CH_2$-4), 2.74 (m, 2 H, $CH_2$-7), 3.28 (br s, 2 H, $NCH_2$), 3.46 (br s, 2 H, $NCH_2$), 4.23 (s, 1 H, HC=), 5.90 (s, 1 H, H-3).

$^{13}$C NMR (101.6 MHz, $CDCl_3$): δ = 13.7 (2 Me), 22.4, 22.5, 22.9, 23.3 ($CH_2$-4,5,6,7), 46.2 (2 $NCH_2$), 80.6 (HC=), 110.9 (C-3), 122.1 (C-4), 126.8 (C-5), 131.5 (C-2), 157.8 (=CN), 167.7 (CO).

MS: *m/z* = 244 [$M^+$].

Anal. Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47. Found: C, 73.69; H, 8.48; N, 11.36.

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