Chemistry and Materials Research
ISSN 2224- 3224 (Print) ISSN 2225- 0956 (Online)
Vol.6 No.1, 2014

A New Road for the Synthesis and Characterization of New Enamino Benzodiazepines

Mohamed Loughzail[1*] Abdesselam Baouid[1] El Hassane Soumhi[2] Mohamed Essaber[1]

1. Laboratoire de Chimie Moléculaire, Faculté des Sciences Semlalia, Université Cadi Ayyad, 2390, 40001 Marrakech, Morocco
2. Equipe de Chimie des Matériaux et de l'Environnement, FSTG-Marrakech, Université Cadi Ayyad, Bd Abdelkrim Khattabi, BP. 549, Marrakech, Morocco

* E-mail of the corresponding author: loughzail@gmail.com

Abstract

We report here the synthesis of a new 1,5-benzodiazepines derivatives by phase transfer catalysis. The structures of these products were investigated and confirmed by ^{1}H, ^{13}C NMR, mass spectroscopic and X-ray diffraction.

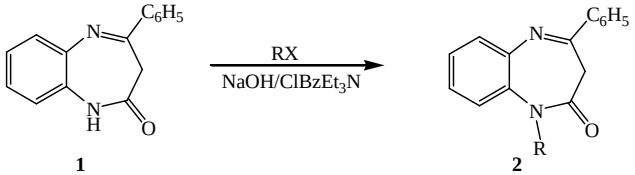
Keywords: Benzodiazepine, N,N-dimethylformamide dimethyl acetal, phase transfer catalysis

1. Introduction

The benzodiazepine nucleus is a pharmacophoric scaffold and represents a class of heterocycles with a wide range of applications. These heterocyclic compounds are important constituents of biologically active products (Heterocyclic Chemistry 1998) and have attracted our considerable attention due to their applications such as pharmaceuticals and synthetic organic chemistry (Comprehensive Heterocyclic Chemistry 1996). In particular, several representative benzodiazepines possess significant biological activity as antimicrobial agents (Kumar et al.2007), antiviral ((a) Merluzzi et al. 1990 (b) Di Braccio et al. 2001), antitumor agents (Werner et al. 1990), analgesic (Di Brassio et al. 1990), antipsychotic agents (Kavita et al. 1988), antifungal (Meerpoel et al. 2005), and may be considered support for the synthesis of more active heterocyclic systems.
In this report, we describe practical protocol for the preparation of new 1,5-benzodiazepines via a C-alkylation by potassium tert-butoxide in tetrahydrofuran in a low temperature and an N-alkylation by sodium hydroxide in the presence of benzyltriethylammonium chloride in room temperature using the technical phase transfer catalysis (PTC). These new heterocyclic system can be susceptible to have pharmacological activity. This work is integrated in the development of our research series 1,4-(1,5)-benzodiazepines ((a) Benelbaghdadi et al. 2007 (b) Baouid et al. 2001 (c) Boudina et al. 2006).

2. Result and discussion

In the first step, we have realized the N-alkylation of 4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **1** with alkyl bromides moderately active secondary in the presence of 50% sodium hydroxide and 2% mol of benzyltriethylammonium chloride in benzene (Scheme 1).



1 **2**

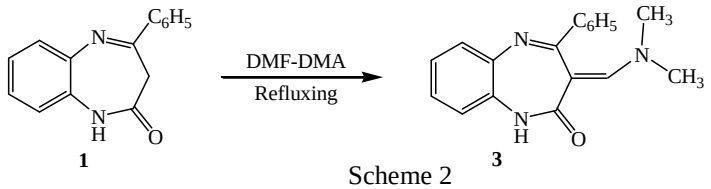
Scheme 1

The compounds **2a-2f** are obtained with excellent yields (Table 1). The structures of the products **2a-2f** were determined by spectral data (mass, ^{1}H, ^{13}C NMR). Analysis, by the X-ray diffraction of compound **2d** (Loughzail et al. 2011), was necessary to elucidate the stereochemistry of the power cycle benzodiazepine.

Table 1: N-Alkylation of 4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **1**

Entry	Products	R-X	Yield (%)
1	**2a**	CH_3-I	90
2	**2b**	$CH_3(CH_2)_4$-Br	94
3	**2c**	$C_6H_5CH_2$-Br	92
4	**2d**	$CHCCH_2$-Br	96
5	**2e**	CH_2CHCH_2-Br	92
6	**2f**	$CH_3CH_2O_2CCH_2$-Br	94

Further, the action of N,N-dimethylformamide-dimethyl acetal (DMF-DMA) in 4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **1** at reflux leads to the formation of 3-[(dimethylamino)methylidene]-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **3** with a good yield of 75% (Scheme 2). Its structure is identified by mass spectral data and NMR (^{1}H, ^{13}C, mass) and the stereochemistry is determined by X-ray diffraction (Figure 1).



1 **3**

Scheme 2

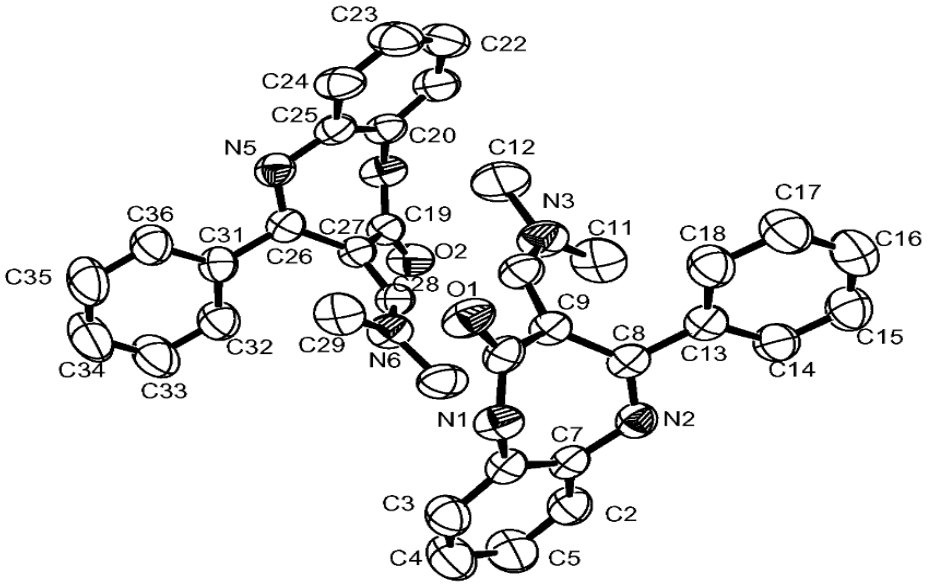
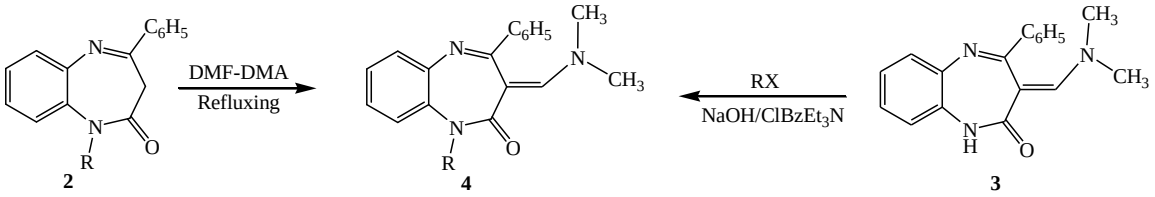


Figure 1**:** Ortep of (E)-3-[(dimethylamino)methylidene]-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **3**

The asymmetric unit of the compound **3** consists of two independent molecules, each having an (E) configuration with respect to the C=C bond between the benzodiazepinone and dimethylamine groups. In the crystal, the two independent molecules are linked into a dimer by a pair of N—H···O hydrogen bonds.

In the second step, we performed the synthesis of compounds **4a-4f** by two synthetic routes using method **A** (DMF-DMA/reflux) and method **B** (RX/PTC) (Scheme 3). Therefore, we adopted the method as A practical protocol for the synthesis of **4a-4f** because it leads to better yields (Table 2). The structures of compounds **4a-4f** are determined from mass spectral data and ^{1}H, ^{13}C NMR. The analysis by X-ray diffraction of product **4d** (Loughzail et al. 2014, Figure 2) confirms the structure and stereochemistry of the heterocyclic system.



Scheme 3

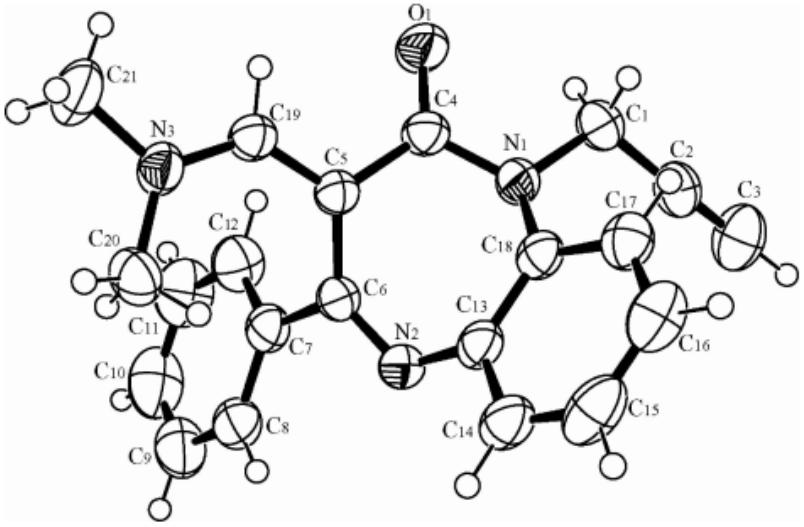
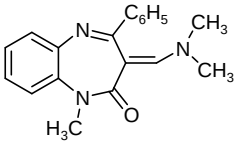
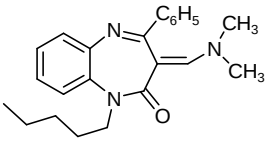
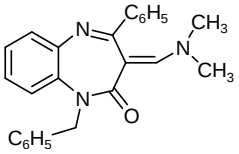
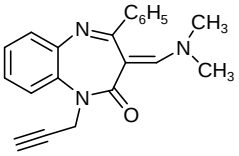
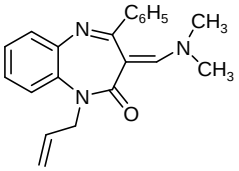
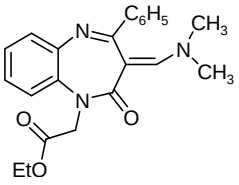


Figure 2: Ortep of (E)-3-[(dimethylamino)methylidene]-4-phenyl-1-(prop-2-ynyl)-1H-1,5-benzodiazepin-2(3H)-one **4d**

The 3-[(dimethylamino)methylidene]-4-phenyl-1-(prop-2-ynyl)-1H-1,5-benzodiazepin-2(3H)-one **4d**, exhibits an (E) configuration with respect to the C=C bond between the benzodiazepine and dimethylamine groups. The seven-membered diazepine ring displays a boat conformation. In the crystal, molecules are linked by a C—H···O hydrogen bond, forming a chain along [110].

Table 2: Synthesis of 1-alkyl-3-dimethylaminomethylidene-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **4**

Entry	Products	Structures	Yield (%)	
			Method A	Method B
1	**4a**		80	62
2	**4b**		68	46
3	**4c**		82	63
4	**4d**		93	70
5	**4e**		92	68
6	**4f**		88	64

All reactions were carried out under optimization conditions.
Method A: DMF-DMA, refluxed at 100 ℃ for 4 h.
Method B: RX, 50% NaOH, 2% $ClBzEt_3N$ (PTC).

3. Conclusion

In summary, we have developed an efficient method for the synthesis of enamino benzodiazepines derivatives. The advantages the presented methodology are efficiency, simplicity, high yield, cleaner reaction profile, easy product isolation, and finally an attractive strategy for the preparation of enamino benzodiazepines compounds.

Experimental Section

General

Melting points were taken in an open capillary tube on a Buchi 510 apparatus and are uncorrected. Spectra were recorded with the following instruments: 1H NMR spectra: Brüker AC-300, 13C NMR spectra: Brüker AC-75, Mass spectra: Jeol JMS DX 300. TMS was used as an internal reference. Column chromatography was carried out using E-Merck silica gel 60F254. Reagents and solvents were purified in the usual way.

General procedure for preparation of 1-alkyl-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one 2a-2f

A mixture of 1 g (4.6 mmol) of 4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **1**, 0.43 g (2.3 mmol) of benzyltriethylammonium chloride and 3 mL of a 50% sodium hydroxide aqueous solution in benzene (25 mL) was stirred at ambient temperature. After 15 min, alkyl bromide was added slowly. After 6 h of stirring at 298 K, the reaction mixture was diluted with water (30 mL). The organic layer was extracted with benzene (3 × 10 mL), dried over anhydrous sodium sulfate and evaporated under vacuum. The title compound was isolated by column chromatography on silica gel using hexane/ethyl acetate as eluent. The solid product was recrystallized in dichloromethane to give of **2a-2f**.

2a Yield 90%. Melting point: 347–349 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.23 (s, 3H, N-CH_3), 2.81 and 4.00 (AB system, d, J= 11.7 Hz, 2H, CH_2), 7.11-8.04 (9H, Ar-H).^{13}C NMR (75 MHz, $CDCl_3$): δ 35.2 (1C, N-CH_3), 40.1 (1C, CH_2), 121.9 - 141.9 (12C, Ar-C), 165.1 (1C, Ph-C=N), 166.7 (1C, CO). MS (EI, m/z): 251$[M+H]^+$.

2b Yield 94%. Melting point: 352–354 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (t, J= 7.2 Hz, 3H, CH_3), 3.02 and 4.17 (AB system, d, J= 12 Hz, 2H, CH_2-CO-N), 7.26-8.04 (9H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6 (1C, CH_3), 19.8, 30.0, 30.1, 46.9 (4C, CH_2), 40.1 (1C, CH_2-CO-N), 122.4 - 131.1 (12C, Ar-C), 165.1 (1C, Ph-C=N), 166.4 (1C, CO). MS (EI, m/z): 307 $[M+H]^+$.

2c Yield 92%. Melting point: 401–403 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 and 4.22 (AB system, d, J= 11.7 Hz, 2H, CH_2-CO-N), 5.14 (s, 2H, N-CH_2), 7.07-8.04 (14H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.0 (1C, CH_2), 51.2 (1C, N-CH_2), 122.4-141.7 (18C, Ar-C), 165.1 (1C, Ph-C=N), 166.4 (1C, CO). MS (EI, m/z): 327 $[M+H]^+$.

2d Yield 96%. Melting point: 438–440 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (t, J= 2.25 Hz, 1H, HC≡C), 3.04 and 4.76 (AB system, d, J=12 Hz, 2H, CH_2-CO-N), 4.19 and 4.27 (AB system, d, J= 17.7 Hz, 2H, N-CH_2-C), 7.25-8.14 (9H, Ar-H).^{13}C NMR (75 MHz, $CDCl_3$): δ 36.9 (1C, N-CH_2-C), 39.1 (1C, CH_2-CO-N), 71.9 (1C, HC≡C), 78.5 (1C, HC≡ C), 120.9-140.9 (12C, Ar-C), 160.0 (1C, Ph-C=N), 165.0 (1C, CO). MS (EI, m/z): 275 $[M+H]^+$.

2e Yield 92%. Melting point: 432–434 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.35 and 4.82 (AB system, d, J=12.15 Hz, 2H, CH_2-CO-N), 4.50 (m, 2H, N-CH_2), 5.15 (m, 2H, CH_2=CH), 5.85 (m, 1H, CH_2=CH), 7.25-8.14 (9H, Ar-H).^{13}C NMR (75 MHz, $CDCl_3$): δ 44.53 (1C, CH_2-CO-N), 50.57 (N-CH_2), 117.56 (CH_2=C), 123.32 (C=CH), 120.9-140.9 (12C, Ar-C), 165.1 (1C, Ph-C=N), 166.4 (1C, CO). MS (EI, m/z): 277 $[M+H]^+$.

2f Yield 94%. Melting point: 418–420 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, J= 7.2 Hz, 3H, CH_3), 3.12 and 4.22 (AB system, d, J= 12 Hz, 2H, N-CH_2), 4.17 and 4.63 (AB system, d, J= 17.1 Hz, 2H, CH_2-CO), 4.24 (q, J= 7.2 Hz, 2H, CH_2), 7.26-8.14 (9H, Ar-H).^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (1C, CH_3), 39.5, 50.6, 61.7 (3C, CH_2), 121.9-141.8 (12C, Ar-C), 166.2 (1C, Ph-C=N), 168.8 (1C, N-CO), 196.2 (1C, CO). MS (EI, m/z): 295 $[M+H]^+$.

Synthesis of (E)-3-dimethylaminomethylene-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one 3

A mixture of 0.47 g (1.98 mmol) of 4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **1** in 4.5 mL of dimethylformamide-dimethylacetal (DMF-DMA) was stirred at 100 ℃ for 4 hours and then cooled to ambient temperature. Filtration and washing with a little cold diethyl ether gave 0.46 g of 3-dimethylaminomethylidene-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **3**. The product obtained was recrystallized from diethyl ether.

3 Yield: 75%. Melting point: 497-498 K. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.55 (s, 6H, $(CH_3)_2N$), 2.80 (s, 1H, NH), 6.32 (s, 1H, C=CH-N), 7.04-7.92 (m, 9H, H-Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 43.50 ($N(CH_3)_2$), 98.02 (C=), 121.47-141.86 (12C-Ar), 151.18 (CH-$N(CH_3)_2$), 167.40 (Ph-C=N), 178.57 (CO). MS (m/z, %): 292 ($[M+H]^+$.

Preparation of 1-alkyl-3-dimethylaminomethylidene-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one 4a-4f

Method A: A mixture of 0.6 g (2.06 mmol) of 3-dimethylaminomethylidene-4-phenyl-1H-1,5-benzo-diazepin-2(3H)-one **3**, 0.1 g (1.03 mmol) of benzyltriethylammonium chloride and 3 mL of a 50% sodium hydroxide aqueous solution in benzene (25 mL) was stirred at ambient temperature. After 15 min, alkyl bromide was added slowly. After 8 h of stirring at 298 K, the reaction mixture was diluted with water (30 mL). The organic layer was extracted with benzene (3 × 10 mL), dried over anhydrous sodium sulfate and evaporated under vacuum. The title compound was isolated by column chromatography on silica gel using hexane/ethyl acetate as eluent. The solid product was recrystallized in dichloromethane to give **4a-4f**.

Method B: A mixture of 0.50 g of 1-alkyl-4-phenyl-1H-1,5-benzodiazepin-2(3H)-one **2a-2f** in 4.5 mL of DMF-DMA was stirred at 100 ℃ for 4 hours and then cooled to ambient temperature. Filtration and washing with a little cold diethyl ether gave 1-alkyl-3-dimethylaminomethylidene-4-phenyl-1H-1,5-benzo- diazepin-2(3H)-one **4a-4f**. The product obtained was recrystallized from diethyl ether.

4a Yield 80%. Melting point: 473–477 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 6H, $(CH_3)_2N$), 3.28 (s, 3H, NCH_3), 6.32 (s, 1H, C=CH-N), 7.16-8.02 (9H, H-Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.5 (NCH_3), 42.8 ($N(CH_3)_2$), 98.3 (C=), 120.9-150.2 (12C-Ar, N-CH=), 176.3 (CO). MS (m/z, %): 306 ($[M+H]^+$.

4b Yield 68%. Melting point: 479–481 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J= 7.2 Hz, 3H, CH_3), 2.64 (s, 6H, $(CH_3)_2N$), 6.22 (s, 1H, C=CH-N), 7.16-8.02 (9H, H-Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.6 (1C, CH_3), 19.9, 30.3, 30.4, 47.1 (4C, CH_2), 42.8 ($N(CH_3)_2$), 98.3 (C=), 120.9-150.2 (C-Ar, N-CH), 165.1 (1C, Ph-C=N), 176.6 (CO). MS (m/z, %): 362 ($[M+H]^+$.

4c Yield 82%. Melting point: 484–486 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58 (s, 6H, $(CH_3)_2N$), 4.81 and 5.30 (AB system, d, J= 15Hz, 2H, CH_2-N), 6.46 (s, 1H, C=CH-N), 7.01-7.93 (14H, H-Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.6 ($N(CH_3)_2$), 49.0 (1C, N-CH_2), 97.4 (C=), 136.6-145.9 (C-Ar, =CH), 165.5 (1C, Ph-C=N), 173.9 (CO). MS (m/z, %): 382 ($[M+H]^+$.

4d Yield 93%. Melting point: 488–490 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (t, J= 2.27 Hz, 1H, HC≡C), 2.58 (s, 6H, $(CH_3)_2N$), 4.21 and 4.29 (AB system, d, J= 17.9 Hz, 2H, N-CH_2-C), 6.46 (s, 1H, C=CH-N),7.15-8.11 (9H, Ar-H).^{13}C NMR (75 MHz, $CDCl_3$): δ 37.1 (1C, N-CH_2-C), 42.6 ($N(CH_3)_2$), 71.9 (1C, HC≡C), 78.5 (1C, HC≡ C), 97.8 (C=), 120.9-140.9 (Ar-C, =CH), 164.8 (1C, Ph-C=N), 169 (1C, CO). MS (EI, m/z): 330 $[M+H]^+$.

4e Yield 92%. Melting point: 480–482 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.79 (s, 6H, $(CH_3)_2N$), 4.42 (m, 2H, N-CH_2), 5.14 (m, 2H, CH_2=CH), 5.83 (m, 1H, CH_2=CH), 6.36 (s, 1H, C=CH-N), 7.1-8.02 (9H, H-Ar).^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.8 ($N(CH_3)_2$), 50.0 (1C, N-CH_2), 98.4 (C=), 116.7 (CH_2=C), 116.6-149.9 (C-Ar, =CH, N-CH), 165.7 (1C, Ph-C=N), 172.9 (CO). MS (m/z, %): 332 ($[M+H]^+$.

4f Yield 88%. Melting point: 460–462 K. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, J= 7.2 Hz, 3H, CH_3), 2.79 (s, 6H, $(CH_3)_2N$), 3.95 and 4.58 (AB system, d, J= 17.1 Hz, 2H, CH_2-CO),4.21 (q, J= 7.2 Hz, 2H, CH_2), 6.32 (s, 1H, C=CH-N), 7.04-7.92 (9H, H-Ar). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1 (1C, CH_3), 42.8 ($N(CH_3)_2$), 51.1 (1C, O-CH_2), 61.2 (1C, N-CH_2), 98.0 (C=), 121.5-150.2 (C-Ar, N-CH), 165.7 (1C, Ph-C=N), 169.9 (CO), 175.1 (O-CO). MS (m/z, %): 378 ($[M+H]^+$.

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