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Synthesis of 1,3,3a,5-Tetraaryl-3a,4,5,6-tetrahydro-3*H*-1,2,4-triazolo[4,3-*a*][1,5]benzodiazepines

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ABSTRACT: *A series of 3a,5-diaryl-1,3-diphenyl-3a,4,5,6-tetrahydro-3H-1, 2,4-triazolo[4,3-a][1,5]benzodiazepines was synthesized by the cycloaddition reactions of 2,4-diaryl-2,3-dihydro-1H-1,5-benzodiazepines and N-phenylbenzonitrileimine generated from N-phenylbenzenecarbohydrazonic chloride in the presence of triethylamine in anhydrous tetrahydrofuran.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:557–559, 2001

INTRODUCTION

Among tricyclic benzodiazepine derivatives, triazolobenzodiazepines are one of the most important families due to their pharmaceutical interest [1–5]. Several triazolobenzodiazepines, e.g. triazolam, estazolam, and flumazenil were found to be effective in the treatment of some CNS disturbances [1]. Alprazolam and triazolam were shown to have clinically useful anxiolytic and hypnotic activity [2–4]. Several triazolobenzodiazepines have been evaluated as antagonists of platelet activating factor [5]. Hence, a number of synthetic methods have been developed in recent years [6,7], providing interesting and useful routes to annulated 1,4-benzodiazepines [8]. Up to now, much attention has been paid to the synthesis of 1,2,4- triazolo[1,4]benzodiazepines by various methods [9–12]. However, only a few of the 1,2,4-triazole-fused 1,5-benzodiazepine derivatives have been reported [13–16]. In recent years, our working group has synthesized numerous 1,5-benzothiazepine and 1,5-benzodiazepine tricyclic derivatives and studied their stereostructures and spectral properties due to their biological and pharmaceutical importance [17–20]. As a continuation of our work on the cycloadditions of 1,5-benzoheteroazepines, herein we report the cycloadditions of 2,4-diaryl-2,3-dihydro-1*H*-1,5-benzodiazepines with *N*-phenylbenzonitrileimine.

RESULTS AND DISCUSSION

Although several synthetic methods have been developed for 1,2,4-triazole-fused 1,5-benzodiazepine derivatives [13–16], in connection with our investigation of the cycloaddition reactions of 1,5-benzodiazepines and 1,5-benzothiazepines, we have tested the 1,3-dipolar cycloaddition of 1,5-benzodiazepines with a nitrileimine for synthesis of 1,2,4-triazolo[4,3-*a*][1,5]benzodiazepines (Scheme 1).

2,4-Diaryl-2,3-dihydro-1*H*-1,5-benzodiazepines (**1a–f**) were synthesized from *o*-phenylenediamine and α,β-unsaturated ketones in good yields [17,20]. *N*-Phenylbenzenecarbohydrazonic chloride was prepared from N′-benzoylphenylhydrazine and phosphorus pentachloride. 1,5-Benzodiazepines (**1a–f**) reacted with *N*-phenylbenzonitrileimine, generated from *N*-phenylbenzenecarbohydrazonic chloride in the presence of triethylamine in anhydrous tetrahydrofuran, to give the new 3a,5-diaryl-1,3-diphenyl-3a,4,5,6-tetrahydro-3*H*-1,2,4-triazolo[4,3-*a*][1,5] benzodiazepines (**2a–f**) in low to moderate yields.

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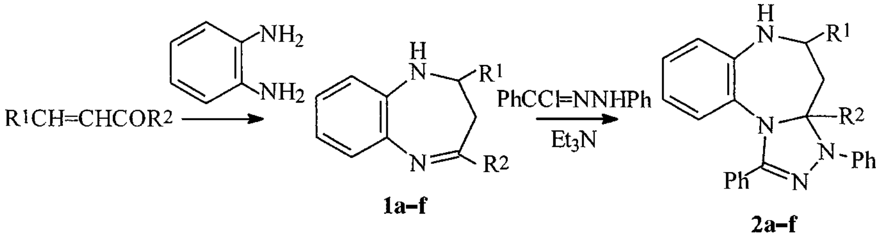

SCHEME 1 Synthesis of 3a,5-diaryl-1,3-diphenyl-3a,4,5,6-tetrahydro-3*H*-1,2,4-triazolo[4,3-*a*][1,5]benzodiazepines.

Their structures were confirmed by ^{1}H NMR, MS, IR, and elemental analyses. In their IR spectra, the absorption of C=N (about 1610 cm^{-1}) in the benzodiazepine ring had disappeared (Tables 1 and 2).

In order to improve the yield, we have carried out the reaction in different solvents (THF, Et_2O, and benzene) at various temperatures (RT and with refluxing). Unfortunately, all attempts were unsuccessful. After studying the obtained adducts, we found that the adducts are unstable in solution, for instance, in chloroform, tetrahydrofuran, diethyl ether, benzene, etc. Even when determining their ^{1}H NMR spectra, they must be dissolved in $CDCl_3$ prior to the spectral determination. If not, no satisfactory spectrum was obtained due to their instability. They even decompose partly in solution at room temperature. This rationalizes the reason why the yields are so low in this cycloaddition.

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. Elemental analyses were carried out on an Elementar

TABLE 1 Physical and Spectral Data

Compd.	*R^1*	*R^2*	*Yield (%)*	*m.p.(°C)*	*^{1}H NMR (CDCl$_3$/TMS) δ (ppm), J (Hz)*	*MS m/z (m$^+$)*
2a	2-BrPh	Ph	18	137–139	2.79 (1H, dd, *J* = 11.1, 13.8), 3.07 (1H, d, *J* = 13.8), 3.70 (1H, s, br, NH), 4.84 (1H, d, *J* = 11.1), 6.68–7.89 (23H, m, aromatic)	570
2b	Ph	4-ClPh	26	258–260	2.89 (1H, dd, *J* = 10.5, 14.4), 2.91 (1H, d, *J* = 14.4), 3.86 (1H, s, br, NH), 4.25 (1H, d, *J* = 10.5), 6.60–7.73 (23H, m, aromatic)	526
2c	2-MeOPh	Ph	17	259–261	2.69(1H, dd, *J* = 10.3, 11.7), 3.02 (1H, d, *J* = 10.3), 3.79 (3H, s, MeO), 3.80 (1H, s, br, NH), 4.84 (1H, d, *J* = 11.7), 6.60–7.96 (23H, m, aromatic)	522
2d	Ph	4-MeOPh	34	225–228	2.83 (1H, dd, *J* = 9.3, 13.2), 2.93 (1H, d, *J* = 13.2), 3.79 (3H, s, MeO), 3.85 (1H, s, br, NH) 4.31 (1H, d, *J* = 9.3), 6.60–7.70 (23H, m, aromatic)	522
2e	3-ClPh	Ph	26	155–158	2.82 (1H, dd, *J* = 10.8, 14.1), 3.00 (1 H, d, *J* = 14.1), 3.82 (1H, s, br, NH), 4.32 (1H, d, *J* = 10.8), 6.60–8.00 (23H, m, aromatic)	526
2f	2-ClPh	Ph	18	135–138	2.77 (1H, dd, *J* = 11.1, 13.5), 3.07 (1H, d, *J* = 13.5), 3.71 (1H, s, br, NH), 4.88 (1H, d, *J* = 11.1), 6.60–7.90 (23H, m, aromatic)	526

TABLE 2 Elemental Analysis Data

			Cald.			*Found*		
Compd.	*Molecular Formula*	*Molecular Weight*	*C*	*H*	*N*	*C*	*H*	*N*
2a	$C_{34}H_{27}N_4Br$	571.51	71.45	4.76	9.80	71.09	4.49	9.57
2b	$C_{34}H_{27}N_4Cl$	527.06	77.48	5.16	10.63	77.57	5.37	10.44
2c	$C_{35}H_{30}N_4O$	522.64	80.43	5.79	10.72	80.77	5.39	10.70
2d	$C_{35}H_{30}N_4O$	522.64	80.43	5.79	10.72	80.31	5.41	10.67
2e	$C_{34}H_{27}N_4Cl$	527.06	77.48	5.16	10.63	77.13	5.05	10.30
2f	$C_{34}H_{27}N_4Cl$	527.06	77.48	5.16	10.63	77.22	5.47	10.29

Vario EL elemental analyzer. The ^{1}H NMR spectra were recorded on a Varian Inova 300 spectrometer with TMS as an internal standard in $CDCl_3$. Samples must be dissolved in $CDCl_3$ prior to their spectral determination. The IR spectra were taken on a Brucker Vector 22 FT-IR spectrophotometer in KBr. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. TLC separations were performed on silica gel G plates with petroleum ether (60–90°C)/acetone (8:1) as the eluent, and the plates were visualized with UV light and/or iodine vapor.

Synthesis of 3a,5-diaryl-1,3-diphenyl-3a,4,5,6-tetrahydro-3H-1,2,4-triazolo[4,3-a][1,5]benzodiazepines

General Procedure. To a stirred solution of the 1,5-benzodiazepine derivative **1** (3 mmol) and the *N*-phenylbenzenecarbohydrazonic chloride (0.69 g, 3 mmol) in anhydrous tetrahydrofuran (25 ml), a solution of dried triethylamine (0.609 g, 6 mmol) in anhydrous tetrahydrofuran (6 ml) was added dropwise. The mixture was refluxed for 10–20 h, the optimum reaction time being determined by TLC monitoring (silica gel). Triethylamine hydrochloride was filtered off, the solvent was evaporated at reduced pressure, and the residue was separated on a silica gel column with petroleum ether (60–90°C)/acetone (8:1) as the eluent to give yellowish crystals of **2** after recrystallization from methanol.

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