A Synthesis of Highly Functionalized Pyrido[2,1-*d*][1,2,5]triazepines

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Abstract: A synthesis of functionalized 1-(alkylamino)-4-aryl-2,3-dihydro-2-phenylpyrido[2,1-*d*][1,2,5]triazepines from the sequential reaction between pyridinium ylides, alkyl isocyanides, and 1-[chloro(aryl)methylene]-2-phenylhydrazines in CH_2Cl_2, in good yields, is described.

Keywords: pyrido[2,1-*d*][1,2,5]triazepine, hydrazonoyl chloride, alkyl isocyanide, pyridinium ylide, MCR

Heterocyclic compounds have a special place among natural products and synthetic compounds. More specifically, nitrogen heterocycles are abundant in nature existing in many natural products such as vitamins, hormones, antibiotics, and alkaloids.[1] As useful reaction intermediates, the heterocyclic compounds have found widespread application in organic synhhesis,[2–4] and some of them are active drugs with important application in pharmacology.[5–7]

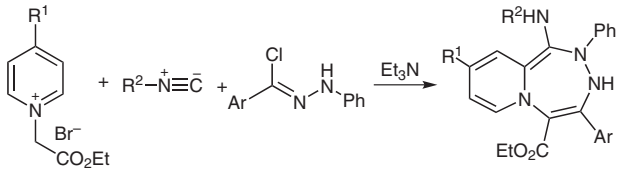
In particular, seven-membered rings exhibit important bioactivities.[8] For this reason, different derivatives of triazepines have attracted a great deal of attention as starting materials in the synthesis of fused heterocyclic systems with potential pharmacological activities.[9–11] Fused heterocyclic ring systems are important scaffolds in medicinal chemistry. Fused triazepines with a bridgehead nitrogen atom in the molecule exhibit interesting biological properties.[12–14]

Herein, we report a one-pot synthesis of functionalized 1-(alkylamino)-4-aryl-2,3-dihydro-2-phenylpyrido[2,1-*d*]-[1,2,5]triazepines **4** from the reaction between ethoxycarbonylpyridinium bromides **1**, alkyl isocyanides **2**, and 1-[chloro(aryl)methylene]-2-phenylhydrazines **3** in CH_2Cl_2, in good yields (Table 1).[15]

The structures of compounds **4a–h** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra. For example, the ^{1}H NMR spectrum of **4a** exhibited three singlets for the *tert*-butyl (δ = 1.21 ppm) and NH (δ = 9.59 and 10.32 ppm) protons, along with multiplets for the aryl groups. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 21 distinct resonances that confirms the proposed structure. The NMR spectra of **4b–h** are similar to those for **4a** except for the aryl moieties, which exhibited characteristic resonances in appropriate regions of the spectra.

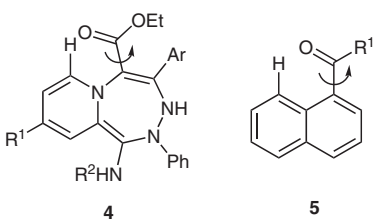
The CH_2O protons of the ester moieties in **4a–h**, as well as the Me_2C and CH_2 protons in **4f–h**, are diastereotopic. Since no asymmetric center is present in **4**, this heterotopicity may be attributed to atropisomerism resulted from slow rotation around the C–CO_2Et single bond in these compounds. Such a rotation is hindered due to the presence of peri interaction between CO_2Et group and the C–H bond of the pyridine moiety (Figure 1), which is expected to be more congested compared to similar interaction in naphthalene derivatives such as **5**.[16] Hindered compounds such as **5** adopt a twisted conformation (i.e., the RCO plane is not coplanar with the naphthalene ring) and may thus exist as a pair of conformational enantiomers. When R is not a prochiral group, the process will be detectable only in the presence of a chiral solvating agent. Thus, an enantiomerization barrier of about 8 kcal/mol has been reported for **5**.[16] The ^{1}H NMR spectra of compounds **4a** and **4f** in 1,2-dichlorobenzene did not show no-

Table 1 Synthesis of Functionalized 1-(Alkylamino)-4-aryl-2,3-dihydro-2-phenylpyrido[2,1-*d*][1,2,5]triazepines **4**



1 2 3 4

Entry	**1–4**	R^1	R^2	Ar	Yield of **4** (%)
1	**a**	H	*t*-Bu	Ph	77
2	**b**	H	*t*-Bu	*p*-tolyl	72
3	**c**	H	*t*-Bu	4-ClC_6H_4	76
4	**d**	Me	*t*-Bu	*p*-tolyl	81
5	**e**	Me	*t*-Bu	4-ClC_6H_4	75
6	**f**	H	1,1,3,3-tetramethylbutyl	Ph	75
7	**g**	H	1,1,3,3-tetramethylbutyl	*p*-tolyl	73
8	**h**	H	1,1,3,3-tetramethylbutyl	4-ClC_6H_4	80



4 5

Figure 1

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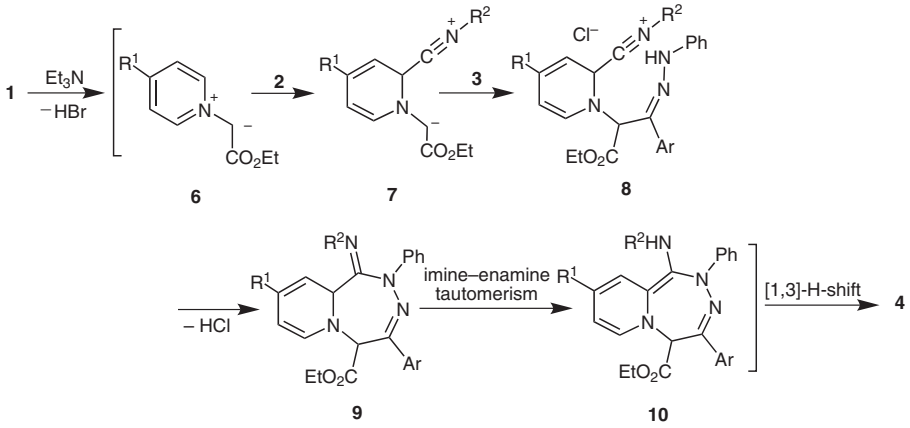

Scheme 1

ticeable broadening, even at 110 °C, the highest temperature investigated. Thus, the conformational racemization barriers for compounds **4** are expected to be higher than 16 kcal/mol.

A mechanistic rationalization for the reaction is given in Scheme 1. The initial event is the formation of nitrogen ylide **6**, which is attacked by alkyl isocyanide to afford the diionic intermediate **7**. This intermediate undergoes a nucleophilic substitution reaction with hydrazonoyl chloride **3** to generate **8**, which affords **9** by intramoleculare cyclization reaction. Intermediate **9** is converted into **4** by imine–enamine tautomerism and [1,3]-H shift.

In summary, we report a tandem transformation involving ethoxycarbonylpyridinium bromides, hydrazonoyl chlorides, and alkyl isocyanides, which affords a new route to the synthesis of functionalized ethyl 1-(alkylamino)-4-aryl-2,3-dihydro-2-phenylpyrido[2,1-*d*][1,2,5]triazepine-5-carboxylates. Due to the presence of transformable functionalities in these products they are potentially valuable for further synthetic manipulations.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **General Procedure for the Synthesis of Compound 4**
To a suspension of **1** (1 mmol) and isocyanide **2** (1 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (2 mmol) at r.t. After stirring for 20 h at r.t., hydrazonoyl chloride **3** (1 mmol) was added to the solution and stirred for 10 h. Subsequently, the solvent was evaporated, and the crude product was washed with EtOAc. The solid mixture was dissolved in CH_2Cl_2 (5 mL) and washed with two 3 mL portions of H_2O, then dried (Na_2SO_4), and evaporated under reduced pressure.
Selected Spectroscopic Data for Compound 4a
Pale yellow powder, mp 148–150 °C, yield 0.34 g, 90%. IR (KBr): ν_{max} = 3419 (NH), 1658, 1548, 1442 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.08 (3 H, t, ^3J = 7.1 Hz, Me), 1.21 (9 H, s, CMe_3), 4.14–4.15 (2 H, m, CH_2O), 6.91 (1 H, t, ^3J = 7.4 Hz, CH), 7.25–7.30 (4 H, m, 4 CH), 7.35–7.38 (2 H, m, 2 CH), 7.60–7.62 (2 H, d, ^3J = 7.7 Hz, 2 CH), 7.79 (1 H, t, ^3J = 6.4 Hz, CH), 7.93 (1 H, t, ^3J = 6.4 Hz, CH), 8.48 (1 H, t, ^3J = 8.1 Hz, CH), 8.73 (1 H, d, ^3J = 6.4 Hz, CH), 8.85 (1 H, d, ^3J = 6.4 Hz, CH), 9.59 (1 H, br s, NH), 10.32 (1 H, br s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 13.9 (Me), 29.9 (CMe_3), 54.7 (C), 60.3 (CH_2O), 105.4 (C), 113.8 (2 CH), 121.0 (2 CH), 124.9 (C), 126.9 (CH), 127.1 (CH), 128.5 (CH), 128.7 (2 CH), 128.9 (2 CH), 130.9 (C), 135.0 (C), 143.8 (CH), 147.2 (CH), 147.5 (C), 148.3 (CH), 153.2 (C), 164.2 (C=O) ppm. MS: *m/z* (%) = 442 (4) [M^+], 411 (75), 355 (77), 290 (28), 77 (100). Anal. Calcd (%) for $C_{27}H_{30}N_4O_2$ (442.24): C, 73.28; H, 6.83; N, 12.66. Found (%): C, 72.84; H, 6.51; N, 12.92.
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