New synthetic route for polymer-supported preparation of benzo[1,4]-diazepin-5-ones with three diversity positions

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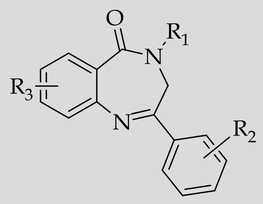
Introduction

Derivatives of 5-substituted-1,3-dihydro-benzo[*e*][1,4]diazepin-2-ones **I** have been studied extensively due to their influence on a central nervous system (CNS). Some of these substances are commercially available drugs.[1] On the other hand, structurally isomeric 2-phenyl-3,4-dihydro-benzo[*e*][1,4]diazepin-5-ones **II** have been studied only rarely. For this reason, we focused on the development of the method of synthesis, preparation, isolation and biological testing of the target compounds with a structure **II**.[2]

I

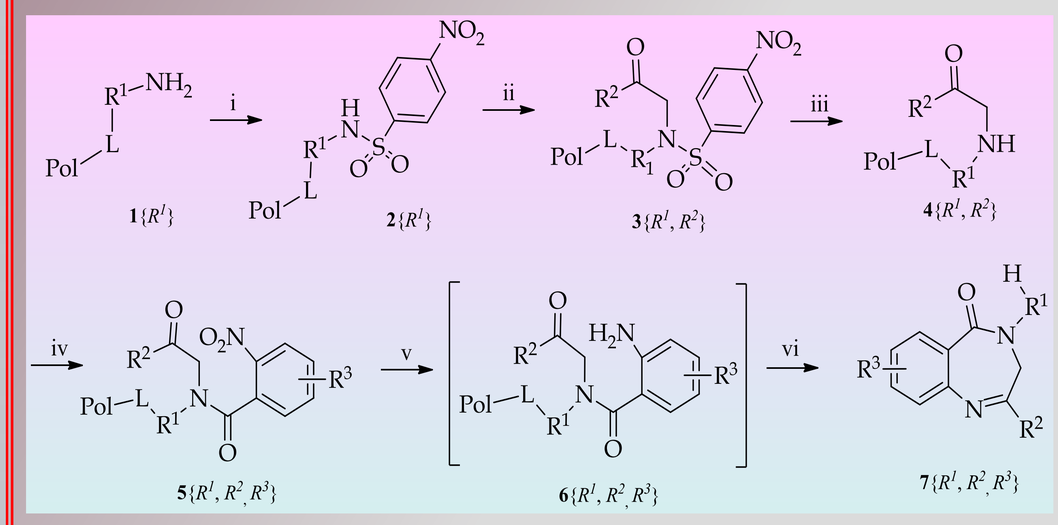


II

Synthesis of target compounds

We present highly-efficient solid-phase synthesis of the final compounds **7** with three diversity position (Scheme 1).[2] It is based on the conversion of polymer supported amines (Figure 1) to α-aminoketones (Figure 2). After the cleavage of the *p*-Nosyl group, the corresponding α-aminoketones were acylated with various *o*-nitrobenzoic acids (Figure 3). Reduction of the nitro group followed by spontaneous on-resin ring closure gave the target immobilized substances.

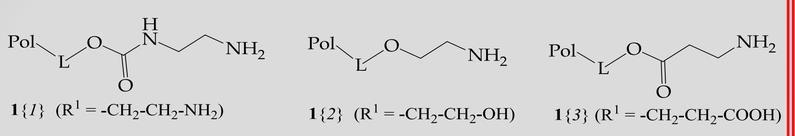
Scheme 1: Developed synthetic route leading to the target benzodiazepines[a]



[a]Reagents: (i) 4-nitrobenzensulfonyl chloride, 2,6-lutidine, DCM, rt, 16 hrs; (ii) bromoketone, DIEA DMF, rt, 16 hrs; (iii) 2-mercaptoethanol, DBU, rt, 10 min; (iv) *o*-nitrobenzoic acids, DIC, DMF, rt, 16 hrs; (v) $SnCl_2 \cdot 2H_2O$, DIEA, deoxygenated DMF, rt, 16 hrs (repeated); (vi) 50% TFA in DCM, rt, 30 min.

Figure 1: List of used immobilized amines 1{*R*[1]}

Wang resin

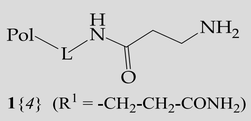


1{*1*} (R^1 = -CH_2-CH_2-NH_2)

1{*2*} (R^1 = -CH_2-CH_2-OH)

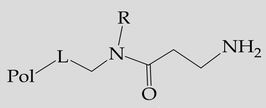
1{*3*} (R^1 = -CH_2-CH_2-COOH)

Rink amide resin



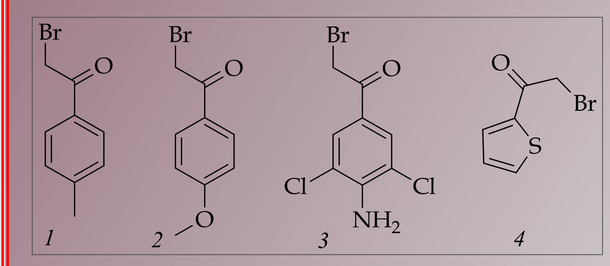
1{*4*} (R^1 = -CH_2-CH_2-$CONH_2$)

BAL resin

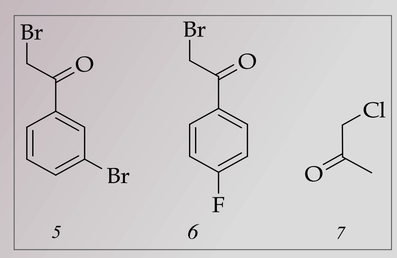


1{*5*} (R = propyl, R^1 = -CH_2-CH_2-CONHPr)
1{*6*}(R = benzyl, R^1 = -CH_2-CH_2-CONHBn)

Figure 2: List of haloketones tested for R^2 substitution

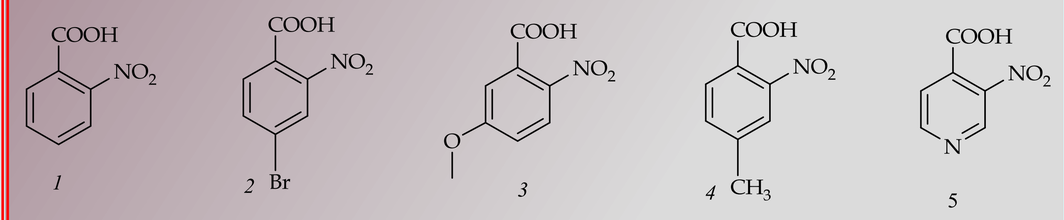


Applicable



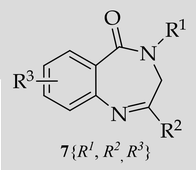
Inapplicable

Figure 3: List of *o*-nitrobenzoic acids tested for R^3 substitution



Trisubstituted benzodiazepinones **7** were obtained in very good crude purity and characterized with ^1H, ^{13}C NMR and HRMS.

Table 1: List of final compounds



7{R^1, R^2, R^3}

Compound	R^1	R^2	R^3	Purity (%)* (after C18)	Purity (%)* (after HPLC)	Yield (%)
7{2,1,1}				97	99	30
7{3,1,1}				72	99	26
7{3,2,1}				93	99	47
7{3,3,1}				88	99	33
7{3,4,1}				83	99	22
7{3,1,2}				85	99	24
7{3,1,3}				73	99	14
7{3,1,4}				87	99	15
7{3,1,5}			Pyridine cycle	76	96	28
7{4,1,1}				79	96	30
7{5,1,1}				96	99	26
7{6,1,1}				85	99	29
7{1,1,1}				77	-	NI
7{1,2,1}				78	-	NI
7{1,3,1}				63	-	NI
7{1,4,1}				58	-	NI

*Calculated from HPLC-UV traces (PDA 200-600 nm), NI = not isolated due to the decomposition during semiprep. HPLC isolation.

Conclusion

We have developed high-througput synthesis of 2-phenyl-3,4-dihydro-benzo[e][1,4]diazepin-5-ones from commercially available building blocks with polymer-supported α-aminoketones being the key intermediates. The solid-phase synthesis concept has been used in order to introduce the methodology applicable for the future preparation of chemical library and subsequent structure-activity relationship studies of the target substances **7**.

[1] L.-H. Sternbach, *J. Med. Chem.* **1979**, *22(1)*, 1-7.
[2] V. Fulopova, T. Gucky, M. Grepl, M. Soural, *ACS Comb. Sci.* **2012**, *14(12)*, 651-656.

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