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4-Chloro-2-Fluoro-5-Nitrobenzoic Acid as a Possible Building Block for Solid-phase Synthesis of Various Heterocyclic Scaffolds

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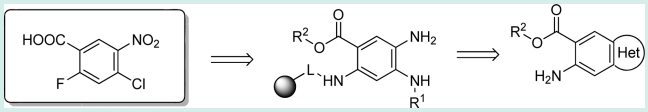
Supporting Information

ABSTRACT: 4-Chloro-2-fluoro-5-nitrobenzoic acid is a commercially available multireactive building block that can serve as a starting material in heterocyclic oriented synthesis (HOS) leading to various condensed nitrogenous cycles. This work describes its ability for the preparation of substituted nitrogenous heterocycles having 5−7-membered cycles via polymer-supported *o*-phenylendiamines. Immobilization of this compound on Rink resin followed by further chlorine substitution, reduction of a nitro group and appropriate cyclization afforded benzimidazoles, benzotriazoles, quinoxalinones, benzodiazepinediones and succinimides. The method developed is suitable for the synthesis of diverse libraries including the mentioned types of heterocycles, which have significant importance in current drug discovery. In this paper, we also report limitation of these method and unsuccessful attempt to prepare an 8-membered benzodiazocine cycle.



KEYWORDS: *solid-phase synthesis, condensed heterocycles, benzimidazoles, benzotriazoles, quinoxalinones, benzodiazepinediones, succinimides*

INTRODUCTION

4-Chloro-2-fluoro-5-nitrobenzoic acid is a commercially available building block that allows large numbers of possible chemical modifications leading to various heterocyclic structures. The advantage of this compound is that the heterocyclic scaffold can be in principle formed on two sides of the molecule, on the "nitro-chloro side" or "carboxy-fluoro side" (structure a in Figure 1), via suitable modification of the appropriate

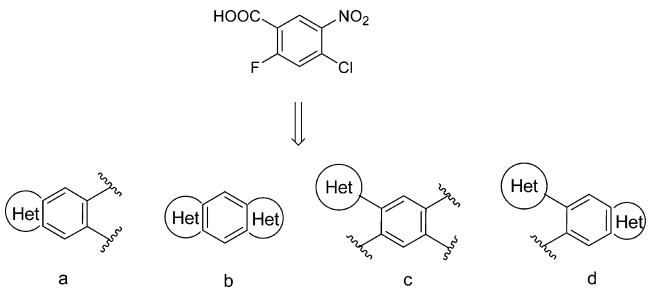


Figure 1. Potential of 4-chloro-2-fluoro-5-nitrobenzoic acid as suitable building block for synthesis of various heterocyclic systems.

groups. Simultaneous (or subsequent) modification of both sides of the molecule can also afford tricyclic bisheterocycles in which two heterocyclic scaffolds are situated at opposite sides of the central benzene ring (structure b in Figure 1). Lastly, there is the possibility to prepare uncondensed heterocycles on the central benzene ring (structure c in Figure 1) and combine this possibility with formation of the condensed system (structure d in Figure 1).

Despite this fact, the application of this acid in chemical synthesis has so far been rare. Its use for the preparation of benzenecarboxamide derivatives as gonadotropin-releasing hormone receptor antagonists is described in a recent patent.[1] The acid was then used in the synthesis of heterocyclic peptides employed in the treatment of hepatitis C virus infection[2] or indazolone sulfonamides as 11β-hydroxysteroid dehydrogenase inhibitors.[3] Another application of this component is reported in work from Feit and Nielson describing the preparation of benzoic acid derivatives useful as diuretics or saluretics.[4] Finally, the component was used by our team for the preparation of hydroxyquinolinones,[5] which is till now the only described solid-phase synthetic method utilizing this building block.

Condensed nitrogenous heterocycles represent a large group of compounds that have been taking an important position in pharmaceutical chemistry for many years. The significant biological and pharmacological properties of such molecules have led to these derivatives being the focus of many investigations. The benzimidazole,[6] benzotriazole,[7] quinoxaline,[8] benzodiazepine[9], and benzodiazocine[10] scaffolds that were selected as target structures in this work are already widely known to have interesting biological properties in drugs currently in the market.

As described above, the condensed heterocycles are still attractive compounds in medicinal chemistry research and that is why, we have decided to explore the applicability of 4-chloro-2-fluoro-5-nitrobenzoic acid for the diversity oriented solid-phase synthesis of compounds that contain various substituted above-mentioned heterocyclic scaffolds. The combination of solid-phase synthesis and diversity oriented synthesis offers a very effective

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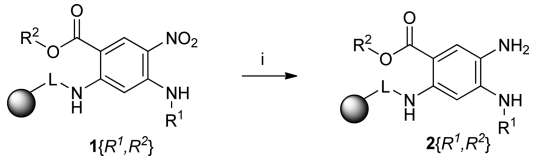
way to get sufficient numbers of compounds of various scaffolds and substitutions in relatively short time for biological screening.

RESULTS AND DISCUSSION

As key-intermediates, *o*-phenylendiamines **2** were prepared according to Scheme 1 by the reduction of the appropriate nitroanthranilates **1** immobilized on Rink amide resin. Preparation of intermediates **1** is described in our previous paper (Scheme 2).[5]

Scheme 1. Preparation of *o*-Phenylendiamine Precursors[a]

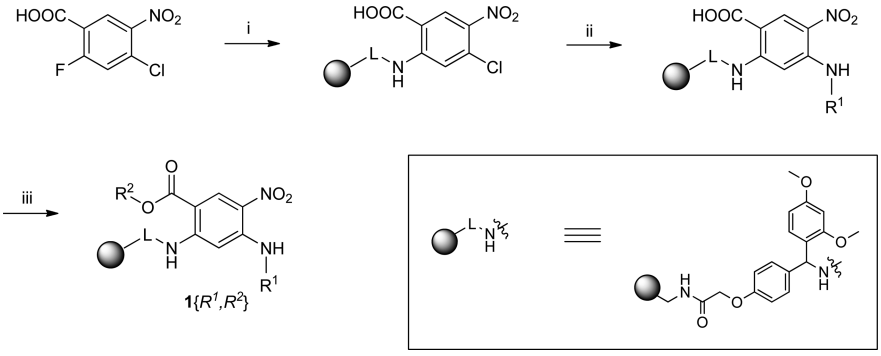


[a]Ssubstituents R^1 and R^2 are defined in Figure 2. Reagents and conditions: (i) $SnCl_2 \cdot 2H_2O$, DBU, DMF, rt, 1 day.

Three primary amines (giving substituents R^1) and two alkylbromides (giving substituents R^2) were used in random combination to verify the synthetic accessibility of the target heterocycles with various substitutions of their scaffold. The combination of the building blocks used is depicted in Figure 2.

Our initial attention was focused on the reduction of nitroanilines **1**. We have already attempted to reduce the nitro to an amino group in our previous work[5] and reported this reaction as unsuccessful. However, later optimization gave promising results when the concentration of tin(II) chloride solution was increased from 1.5 to 2.5 M and the resin was carefully prewashed several times with degassed DMF. Although the reduction took place under the improved conditions, the resulting *o*-phenylendiamines were accompanied with an unknown side product (10−30%, LC-UV traces). Further optimization of the tin(II) chloride method using the base (1,8-diazabicycloundec-7-ene (DBU) instead of *N*,*N*-diisopropylethylamine (DIEA)) eliminated the formation of the side product and all *o*-phenylendiamine derivatives were obtained in an excellent purity (over 90%, LC-UV traces). The reactivity of the diamine intermediates **2** was subsequently studied to form the target heterocycles **3**−**7** (Scheme 3).

Scheme 2. Synthesis of Intermediates 1[a]



[a]Reagents and conditions: (i) 4-chloro-2-fluoro-5-nitrobenzoic acid, DMSO, DIEA, 50 °C, overnight; (ii) amine, DMSO, 120 °C, overnight; (iii) 2-bromoacetophenone, TEA, DMF, rt, overnight or benzylbromide, DIEA, DMF, rt, overnight

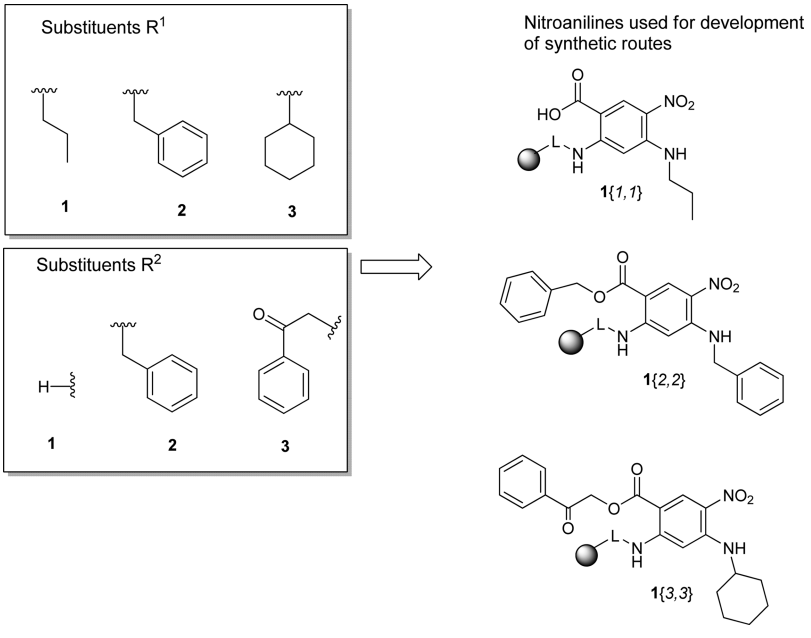


Figure 2. Substituents R^1 and R^2 used for synthesis of starting nitroanilines.

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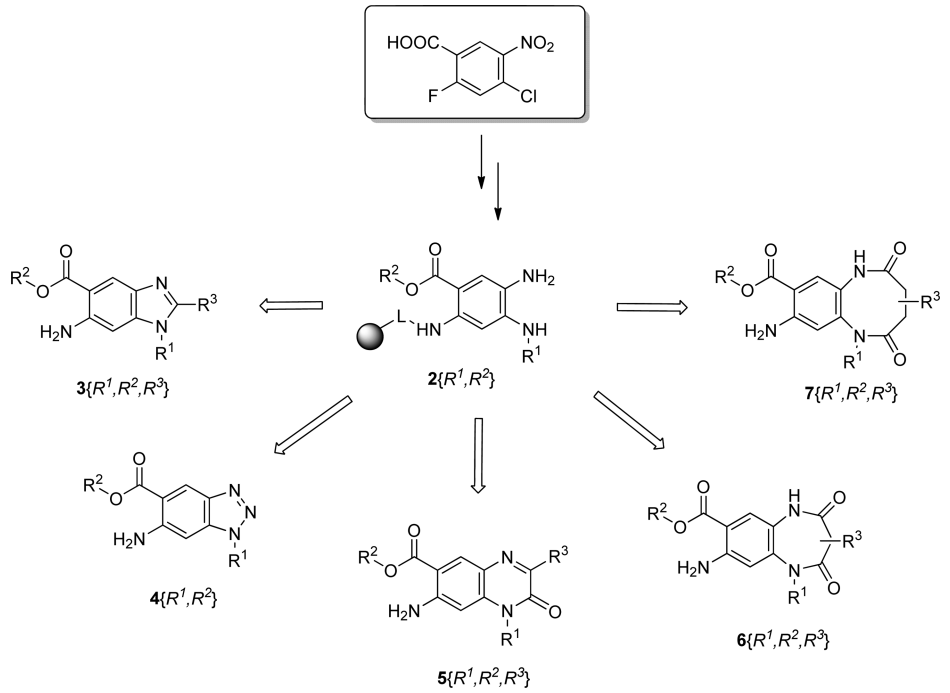
Scheme 3. Intended Use of Immobilized *o*-Phenylendiamine 2{R^1,R^2} for the Preparation of Various Nitrogenous Heterocycles



Benzimidazoles. Solid-phase synthesis of benzimidazoles has become the object of many investigations. The majority of synthetic methods start from the polymer supported *o*-phenylendiamine originating from attachment of 4-fluoro-3-nitrobenzoic acid or dinitrobenzoic acid to a resin via the carboxylic acid group.[11−13] In another method the diamine precursor is attached to the resin via one of the amino groups.[14−16] A different strategy involves the reaction of phenylendiamines with polymer-bound aldehydes or esters.[17,18] All these approaches have been summarized in a review by Kamal.[19] In our work, we applied simple cyclization of immobilized intermediates **2** with aldehydes to afford substituted benzimidazoles **3**. Different aldehydes were tested for this reaction (Figure 3) and their different reactivity was observed.

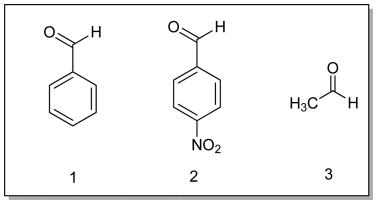
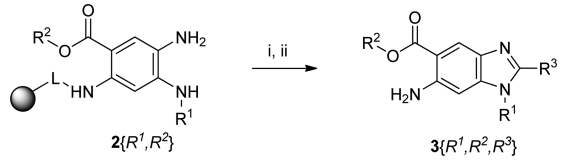


Figure 3. Aldehydes used for the cyclization to benzimidazoles 3{R^1,R^2,1−3}.

Whereas *p*-nitrobenzaldehyde and acetaldehyde easily yielded benzimidazoles 3{*1,1,2*} and 3{*2,2,3*} in DMF after overnight reaction (Scheme 4), the use of unsubstituted benzaldehyde was more complicated. The conversion took place very slowly and afforded the required product with limited purity (about 50%, LC-UV traces). We tried to accelerate the reaction using acidic or basic catalysis or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as a oxidative agent, but each attempt resulted in the undefined mixture of products. Surprisingly, the reaction was significantly improved by the replacement of solvent and benzimidazole 3{*3,3,1*} was achieved in DCM after

Scheme 4. Preparation of Benzimidazoles 3{R^1,R^2,R^3}[a]



[a]Reagents and conditions: (i) aldehyde, DMF, rt, overnight or DCM, reflux, overnight; (ii) TFA/DCM, rt, 1 h.

overnight reflux (Scheme 4). This solvent was then used for preparative synthesis of all three model compounds 3{*1,1,2*}, 3{*2,2,3*}, and 3{*3,3,1*}

Apart from aldehydes, other components such as imidoesters or esters of benzoic acid were tested, but none of these reagents yielded the required benzimidazoles.

Benzotriazoles. Since the benzotriazole moiety performs in organic synthesis as an auxiliary agent in a number of molecular transformations, its application in solid-phase combinatorial chemistry contributes to diverse heterocyclic scaffolds.[20] Katritzky et al. reported a method based on the reaction of polymer-supported *o*-phenylendiamine with isoamyl nitrite.[21] Another article describes the preparation of benzotriazoles from the resin-bound triazene precursors.[22,23] We tried to introduce the nitrogen atom to molecule **2** by means of Katritzky method with isoamyl nitrite, but the reaction afforded product **4** only as part of a mixture with other unidentified compounds.

Optimization of the reaction conditions based on the variation of solvents (DMF and NMP) used, the temperature (reaction was carried out at ambient temperature or at 5 °C) and the reaction time did not increase the purity of the products. Subsequently we decided to use sodium nitrite as a source of the nitrosyl cation (Scheme 5).

Although in this case a long reaction time was needed (four days), model benzotriazoles 4{*2,2*} and 4{*3,3*} were obtained in a high purity (about 90%, LC-UV traces). In the case of the free

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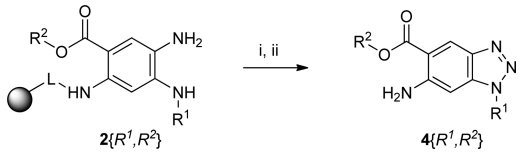
Scheme 5. Preparation of Benzotriazoles 4{R^1,R^2}[a]



[a]Reagents and conditions: (i) $NaNO_2$, AcOH, DMF, rt, 4 days; (ii) TFA/DCM, rt, 1h.

carboxylic acid derivative **2**{*1,1*} reaction did not yield the expected product (according to LC-MS). Thus, target benzotriazole **4**{*1,1*} was achieved using the corresponding benzyl ester **2**{*1,2*} which was hydrolyzed after formation of a triazole ring (Scheme 6).

Quinoxalinones. Quinoxaline derivatives have attracted the attention of many researchers and the literature offers many synthetic pathways carried out on polymer support and providing various derivatives containing the quinoxaline scaffold. In our study we tested several methods leading to structures **5**{R^1,R^2,R^3}(Figure 4).

In solid-phase chemistry immobilized *o*-fluoro-nitrobenzene derivatives are involved in most of the strategies reported. For example Purandare[24] prepared quinoxalinone derivatives with a method based on the reaction of the resin-bound diamine, originating from the reaction of fluoro-nitro derivatives, with carbonyl compounds. Vagner and co-workers acquired quinoxalinone derivatives with a method based on the substitution of *o*-fluoronitrobenzene with polymer-bound amino acid esters. Subsequent reduction of the resulting *o*-nitroanilines yielded dihydroquinoxalinones, which after cleavage from the resin, were air-oxidized to quinoxalinones.[25]

We decided to investigate the application of α-ketocarboxylic acids to obtain quinoxalinone heterocycles. To close the quinoxalinone ring we tested three methods involving a direct acylation, hydroxybenzotriazole (HOBt) activated acylation and an acylation of the nitroanilines **1** with acyl chloride. First we tried a direct acylation of immobilized phenylendiamines **2** with phenylglyoxylic acid. Beside the expected quinoxalinone **5**, we obtained benzimidazole derivative **3** as a side product (Scheme 7).

After thorough investigation of the reaction, we observed that the cyclization to quinoxalinone **5** was highly accelerated by acidic catalysis and thus the formation of undesirable benzimidazole **3** was detected only in low purity (about 20%, LC-UV traces). The choice of the solvent was another factor influencing the outcome of the reaction. Various solvents and reaction temperatures were combined and tested to achieve the model quinoxalinone **5**{*2,2,1*} in as high purity as possible. The best results were obtained at 80 °C in toluene or at reflux in tetrahydrofuran under acetic acid catalysis (Table 1).

These conditions were applied to preparative reaction of diamines **2**{*1,1*}, **2**{*2,2*}, and **2**{*3,3*} with ketocarboxylic acids *1*, *2*, and *3* (Figure 5) to afford model quinoxalinones **5**{*1,1,2*}, **5**{*2,2,3*}, and **5**{*3,3,1*}.

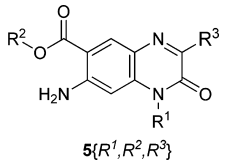


Figure 4. Structures of the aimed quinoxaline **5**{R^1,R^2,R^3}.

Concurrently, we attempted to prepare the target molecule via convenient HOBt activated acylation followed by the condensation of amino and carbonyl groups. We supposed the avoidance of the undesirable decarboxylation and formation of a benzimidazole, but a benzimidazole side product was detected as well (Scheme 7). The third listed method involved a modification of the reaction sequence consisting in the acylation of nitroaniline **1** and subsequent nitro group reduction followed by cyclization (Scheme 8). The reaction of compound **1**{*1,2*} with phenylglyoxilic acid *1* was used as model reaction.

Despite strong deactivation of the amino group caused by the adjacent nitro group in product **1**{*1,2*} we achieved the desired amide intermediate **10**{*1,2,1*} by heating of the resin-bound nitroaniline with acylchloride. Subsequent reduction with tin(II) chloride resulted in final quinoxaline **5**{*1,2,1*} of high purity (95%, LC-UV traces). Unfortunately, this method is not universal for any type of ketocarboxylic acids. In case of acids *2* and *3* (Figure 5) when the formation of their less reactive lactone or anhydride respectively is probably formed initially, the acylation step failed and only starting material was recovered.

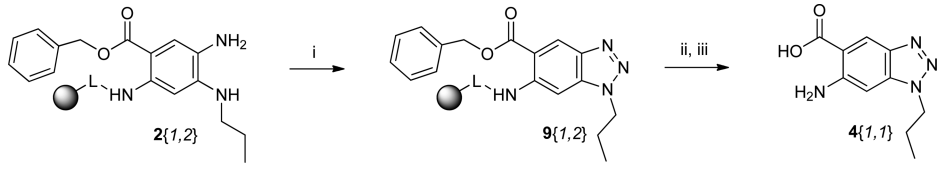
It follows that two of the listed methods, the direct acylation and acylation of nitroanilines, provided quinoxalinones in sufficient purity, but the latter was applicable only with significant limitation concerning the acids used.

Benzodiazepinediones. Although a number of benzodiazepine substructures have been prepared on a polymer-support,[26] a solid-phase synthesis leading to 1,5-benzodiazepine-2,4-diones has not been reported so far.

In our case, malonic acid derivatives were applied to close the 7-membered ring via double acylation of the diamine precursors **2**. We anticipated the simultaneous formation of both amides but the reaction with HOBt-activated acids yielded only acyclic amide **11** with a free carboxylic group (according to LC-MS analysis) and ring closure had to be completed via intramolecular cyclization in next additional step (Scheme 9).

In the case of malonic acid the regioselectivity of the first-step acylation was not determined as both potential structural isomers **11** afford the same product **6**. However, we suppose a preferential acylation of the primary amino group which is in accordance with detailed NMR analysis that has been done with analogical intermediate **14**{*2,2,1*} (Scheme 11). LC-MS analysis revealed that the intermediates **11** were contaminated

Scheme 6. Synthesis of Benzotriazole 4{*1,1*}[a]



[a]Reagents and conditions: (i) $NaNO_2$, AcOH, DMF, rt, 4 days; (ii) potassium trimethylsilanolate, THF, rt, overnight; (iii) TFA/DCM, rt, 1 h.

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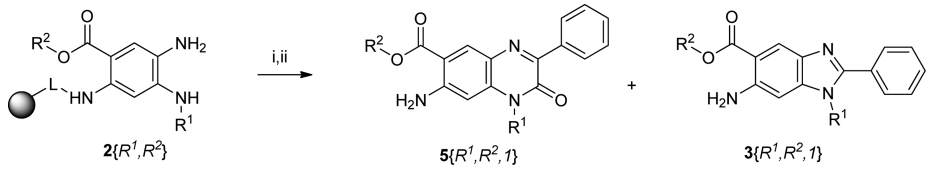
Scheme 7. Synthesis of Quinoxalinones via an Acylation of *o*-Phenylendiamines 2{R^1,R^2} with Phenylglyoxylic Acid[a]



[a]Reagents and conditions: (i) phenylglyoxylic acid, various solvents (Table 1), rt, overnight or 80 °C (reflux for THF), 2 h or phenylglyoxylic acid, HOBt, DIC, DMF/DCM, rt or 5 °C, overnight; (ii) TFA/DCM, rt, 1 h.

Table 1. Solvents Tested for the Preparation of Quinoxalinones 5 (Ratio of Products 5{*2,2,1*} to 3{*2,2,1*} According to LC-UV Traces[a]

	DMF	MeCN	NMP	dioxane	THF	DCM	toluene
rt	1:1	3:2	nt[a]	nt[a]	2:3	1:1	1:2
cat. AcOH, 80 °C[b]	1:1	2:1	1:4	5:1	10:1	nt[a]	10:1

[a]nt = not tested. [b]Reflux for THF.

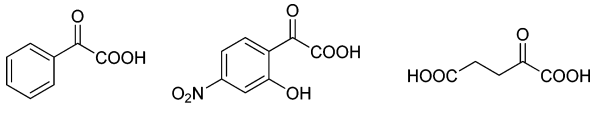


Figure 5. *α*-Ketocarboxylic acids used for the synthesis of quinoxalinones 5{R^1,R^2,*1*−*3*}.

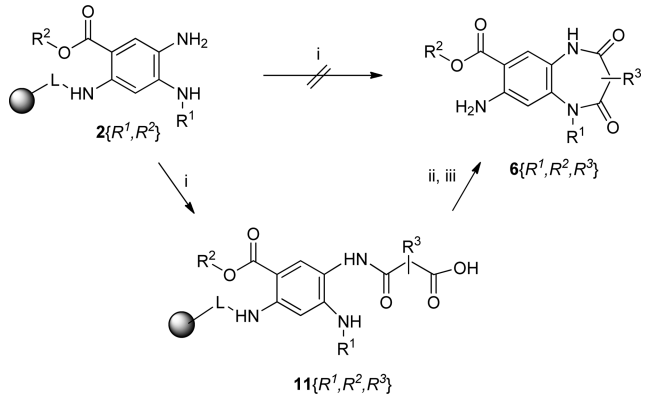
with a side product which was identified as a result of cross-coupling reaction leading to compound **13** (5−30%, LC-UV traces, Figure 6). The structure was verified in case of derivative **13**{*3,3,4*}.

Another noteworthy fact was that the outcome of the first-step acylation reaction was highly dependent on type of the malonic acid used (Figure 7).

Whereas disubstituted malonic acids *4*, *5*, and *6* provided the corresponding intermediates **11**, preparation of an unsubstituted derivative **11**{*3,3,1*} was unsuccessful due to a decarboxylation of the acid during the reaction. Reaction with monosubstituted malonic acids resulted in a mixture of desired carboxy derivative **11**{R^1,R^2,*1*−*3*} and the product of a decarboxylation leading to **12** (Scheme 10).

We tried to suppress the decarboxylation by decreasing the reaction temperature or with use of anhydride formed in situ with use of *N*,*N*-diisopropylcarbodiimide (DIC). However, the starting diamine **2** did not react under such reaction conditions. As another alternative the esterification of the malonic acid was done to avoid the undesired elimination of the carboxylic group. However, after the reaction with the ester of malonic acid only the starting diamines **2** were detected. The harsher reaction conditions

Scheme 9. Two-Step Preparation of Benzodiazepinediones 6{R^1,R^2,R^3}[a]



[a]Reagents and conditions: (i) malonic acid, HOBt, DIC, DMF/DCM, rt, overnight; (ii) HOBt, DIC, THF, 50 °C, 2 h; (iii) TFA/DCM, rt, 1 h.

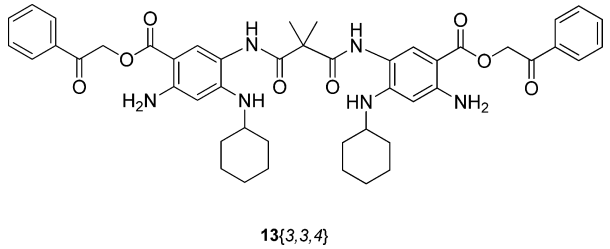
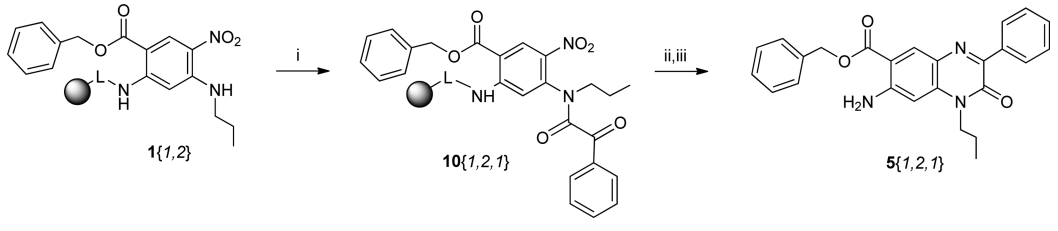


Figure 6. Structure of side products **13**{*3,3,4*}.

achieved by heating in DMSO or DMF yielded a complex mixture. Thus, the applicability of this method is reduced to synthesize only disubstituted derivatives and thus model compounds **11**{*3,3,4*}, **11**{*1,1,5*}, and **11**{*2,2,6*} were prepared.

Neither cyclization step proceeded smoothly. Closing the cycle under mild reaction conditions identical to the first-step acylation provided final heterocycles **6** only with low conversion and significantly contaminated with byproducts. Finally the model benzodiazepindiones **6**{*3,3,4*}, **6**{*1,1,5*}, and **6**{*2,2,6*}

Scheme 8. Formation of Quinoxalinone 5{*1,2,1*} via Acylation of Nitroaniline 1{*1,2*}[a]



[a]Reagents and conditions: (i) phenylglyoxylic acid chloride, DIEA, dichloroethane (DCE), reflux, overnight; (ii) $SnCl_2 \cdot 2H_2O$, DBU, DMF, rt, overnight; (iii) TFA/DCM, rt, 1 h.

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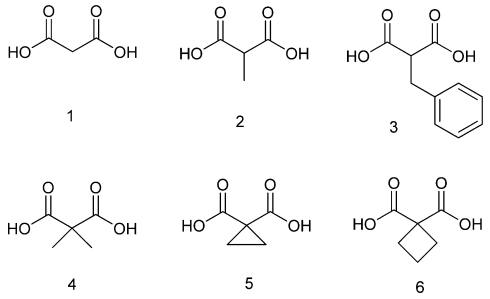


Figure 7. Malonic acids used for the study of preparation of benzodiazepines **6**$\{R^1,R^2,1-6\}$.

were obtained via HOBt acylation in THF at 50 °C. Other methods such as acidic (AcOH) or basic (DIEA) catalysis or the use of alternative activating agents (such as BOP) did not increase the purity.

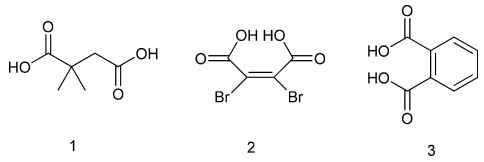
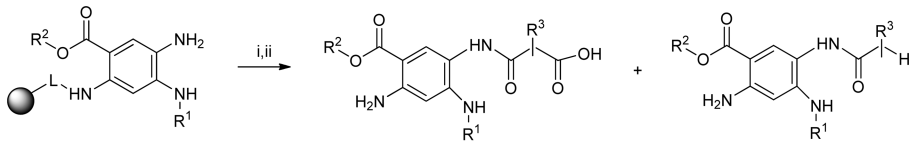


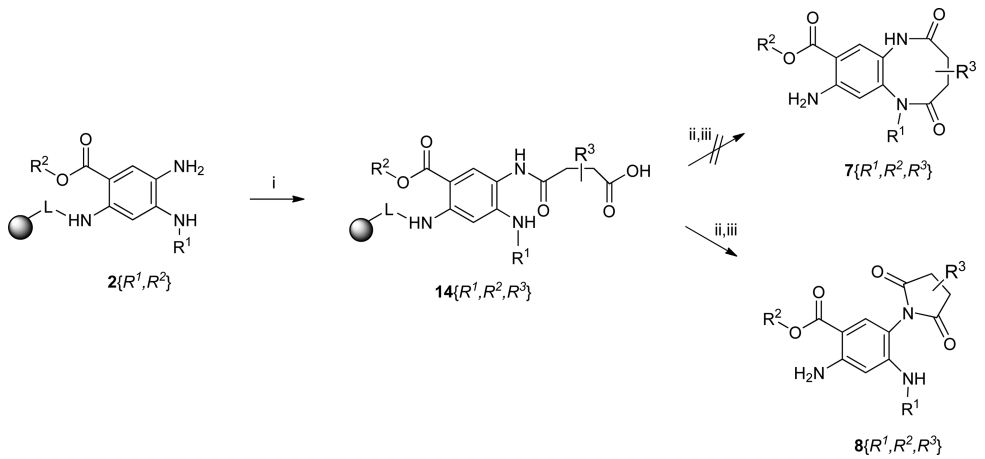
Figure 8. Dicarboxylic acids used for preparation of succinimide, maleimide, and phtalimide **8**$\{R^1,R^2,1-3\}$.

Scheme 10. Acylation of Compounds 11$\{R^1,R^2,R^3\}$ with Unsubstituted and Monosubstituted Malonic Acid[a]



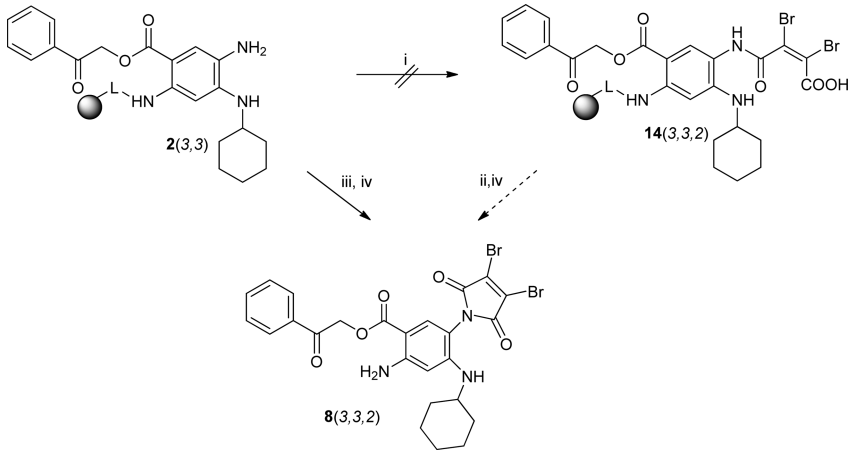
[a]Reagents and conditions: (i) malonic acid, HOBt, DIC, DMF/DCM, rt, overnight; (ii) TFA/DCM, rt, 1 h.

Scheme 11. Unsuccessful Synthesis of Benzodiazocinedione Derivatives 7$\{R^1,R^2,R^3\}$[a]



[a]Reagents and conditions: (i) dicarboxylic acid, HOBt, DIC, DMF/DCM, rt, overnight; (ii) HOBt, DIC, DMF/DCM, rt, overnight; (iii) TFA/DCM, rt, 1h.

Scheme 12. Preparation of Bromo Derivative 8$\{3,3,2\}$[a]



[a]Reagents and conditions: (i) 2,3-dibromomaleinic acid, HOBt, DIC, DMF/DCM, rt, overnight; (ii) HOBt, DIC, DMF/DCM, rt, overnight; (iii) 2,3-dibromomaleic acid, DIC, DMF/DCM, rt, overnight, then the process was repeated; (iv) TFA/DCM, rt, 1 h.

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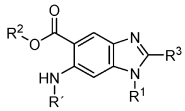
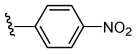
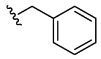
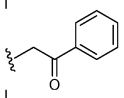
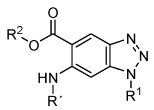
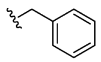
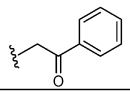
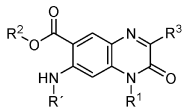
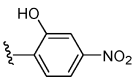
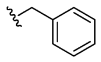
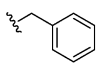
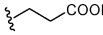
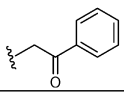
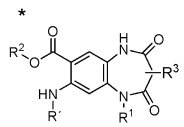
Attempt to Prepare Benzodiazocinediones. After the successful formation of 7-membered ring, we tried to extend the methodology for the preparation of 8-membered rings. Despite various published approaches leading to condensed nitrogenous

Table 2. Summary of the Prepared Compounds

Scaffold	Product	R^1	R^2	R^3	R′	Purity (%)[a]	Yield (%)[b]
	**3**{*1,1,2*}					75	35
	3{*2,2,3*}					60	11
	3{*3,3,1*}					70	37
	**4**{*1,1*}			-		85	75
	4{*2,2*}			-		95	45
	4{*3,3*}			-		90	42
	**5**{*1,1,2*}					90	20
	5{*2,2,3*}					95	53
	5{*3,3,1*}					80	28
* 	**6**{*1,1,5*}					90	19
	6{*2,2,6*}					78	20
	6{*3,3,4*}					50	17
*	**8**{*1,1,3*}					80	22
	8{*2,2,1*}					67	24
	8{*3,3,2*}					77	18

[a]Purity of a crude product (LC-UV traces). [b]Yield of a product after purification (HPLC chromatography). *In the case of derivatives **6**{*1,1,S*} and **8**{*1,1,3*}, acylation of an amino group with TFA was observed during the cleavage from the polymer-support using TFA/DCM.

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8-membered ring derivatives[27−30] the solid-phase method for the preparation of such compounds have not been described.

The double acylation with dicarboxylic acids (Scheme 11) was carried out in two steps as in the case of benzodiazepines **6**.

Surprisingly the second-step acylation took place very smoothly (according to LC-MS analysis) in comparison to the cyclization of intermediates **11**. However, 2D NMR analysis experiments revealed formation of 5-membered cycle **8** instead of the target 8-membered cycle **7** (Scheme 11). Preparation of bromoderivative **14**{*3,3,2*} with use of HOBt activation yielded an unidentified mixture of compounds. In this case the cyclization was performed by one step acylation with the acid anhydride formed in situ with use of DIC (Scheme 12).

Three dicarboxylic acids of aliphatic and aromatic structure (Figure 8) were used at this step. The formation of succinimide, maleimide and phtalimide was verified on three model compounds **8**{*1,1,3*}, **8**{*2,2,1*}, and **8**{*3,3,2*}.

Although considerable limitations were revealed and in some cases moderate yields were obtained, the set of novel heterocyclic derivatives was prepared (Table 2).

CONCLUSION

This study was focused on the reactivity of the commercially available 4-chloro-2-fluoro-5-nitrobenzoic acid and its applicability in the preparation of various condensed nitrogen heterocycles via polymer-supported *o*-phenylendiamines. After careful optimization of the reaction conditions synthetic pathways leading to 5-, 6-, and 7-membered heterocycles were developed and some limitation were described. The preparation of 8-membered heterocycles was unsuccessful and 5-membered succinimide, maleimide and phtalimide were formed instead. The solid-phase synthesis approach applied in this project allows an efficient use of the protocol for diversity oriented synthesis of various heterocycles, as well as for target oriented synthesis of variously substituted privileged heterocyclic scaffold. Since the prepared derivatives represent heterocyclic analogues of anthranilic acid, they can be used also for a synthesis of more complex (poly)heterocyclic structures. The methodology can be applied for the synthesis of a chemical library affording new derivatives for high throughput screening.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and NMR spectra are available. These information are available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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