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A convenient synthesis of 4-aminoaryl substituted cyclic imides

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Abstract—An efficient one-step synthesis of 4-nitro-*N*-aryl substituted glutarimides, succinimides and maleimides in polyphosphoric acid is described together with the subsequent reduction to the corresponding anilines. The scope and limitation of this cyclocondensation are presented.

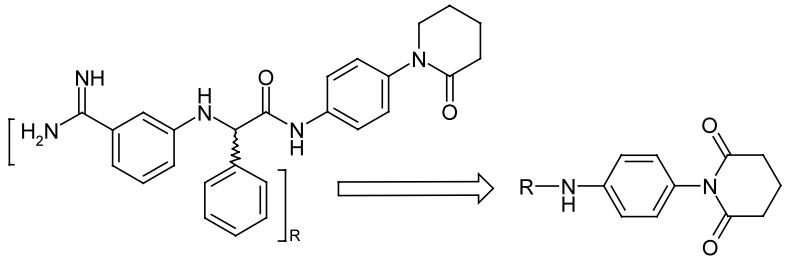
As part of our research program to obtain new inhibitors of coagulation factor Xa (fXa), we have synthesized and evaluated 4-aminophenylpiperidones (surrogates for the S4 binding pocket) such as benzamidine **1a**.[1] In order to extend the scope of this class of compounds, cyclic imides of type **1b** were envisaged (Fig. 1).

N-Substituted cyclic imides are key moieties in naturally occurring alkaloids and in synthetic compounds that have antispasmodic effects[2] and show antinociceptive properties,[3] respectively.

The formation of *N*-substituted cyclic imides has been studied comprehensively and some procedures have been developed and implemented. Most of the transformation to such ring structures involves a three-step synthesis: (1) reaction of a cyclic anhydride with an aniline, (2) conversion of the intermediate monoamide to an activated ester with *N*,*N*′-disuccinimidyl oxalate,[4] acetic anhydride[3,5,6] or thionyl chloride,[7] and (3) thermal and chemical dehydration to the corresponding cyclic imides. One of the precedents utilized aromatic diamines which afforded the respective 2-aminoaryl derivatives in one step.[8] However, cyclic anhydrides were applied in all cases.

In an attempt to prepare 4-chloroimidazo[4,5-*c*]-pyridines with a butyric acid side chain in the 2 position, we have found that the conversion of 2-chloro-3,4-diaminopyridine **2** with glutaric acid **3a** in hydrogen chloride unfortunately led to the 4-oxo compound **4** in high yield (Scheme 1). However, utilizing polyphosphoric acid (PPA), only cyclic imide **5** could be obtained in moderate yield. This is obviously due to the nature of PPA, which usually has a phosphorus pentoxide content of 82–85% and is therefore a versatile acidic dehydrating reagent.[9] This result led us to investigate the generality of this reaction.

Herein, we report on the use of PPA as a more suitable and convenient reagent to prepare *N*-aryl substituted



1a fXa (IC_{50}) = 14.0 nM **1b**

Figure 1. Representative potent fXa inhibitor **1a** and his putative congener **1b**.

Keywords: condensations; cyclisation; *N*-imides; nitro compounds.

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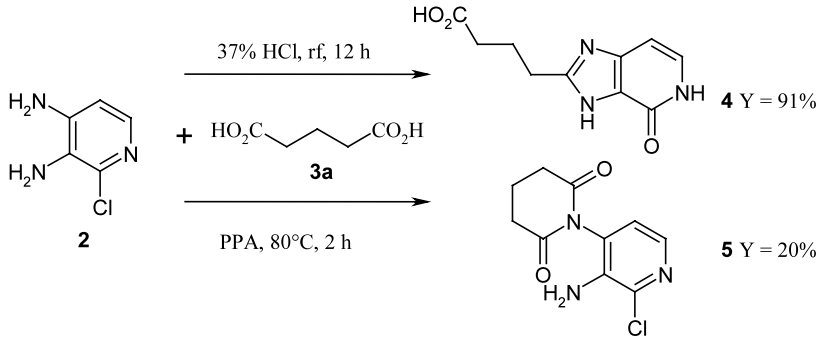


Scheme 1. Selective reaction of compound **2** with glutaric acid **3a** to **4** or **5**, respectively.

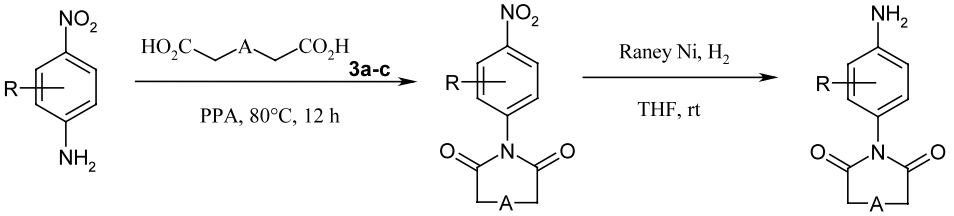
cyclic imides from diacids. The scope and limitation of this reaction are presented together with the subsequent reduction of the intermediate nitro compounds.

We initially investigated the effect of PPA on the reaction of dicarboxylic acids **3a–c** with different 4-nitroanilines **6a–j**, and the results are summarized in Table 1.

As shown in Table 1, amidation and following ring closure afforded cyclic imides **7a–p** in excellent yields and purities.[10] Heating the respective 4-nitroanilines at 80°C for 12 h in polyphosphoric acid the desired glutar- and succinimides were prepared in one step, respectively. The condensation proceeded smoothly for anilines bearing either an electron withdrawing or an electron donating group at the 2 or 3 position.

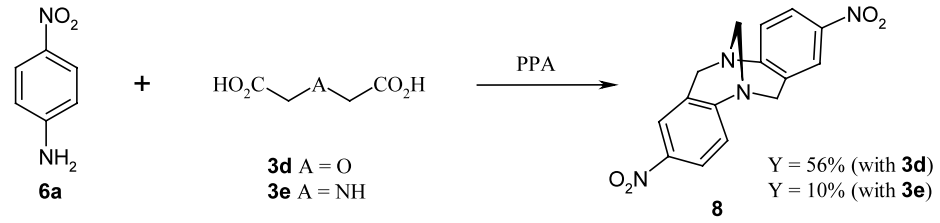
In order to test the influence of the substitution pattern of the dicarboxylic acids some selected, commercially available diacids were reacted with 4-nitroaniline **6a** under standard conditions. 3,3-Dimethylglutaric acid **3c** could be converted to the glutarimide **7c** in high yield whereas the 3-phenyl derivative failed in this reaction (data not shown). However, with diglycolic acid **3d** and iminodiacetic acid **3e** a new route to C_2-symmetric analogues of Tröger's base was discovered.[11] Both acids underwent exclusively condensation with 4-nitroaniline **6a** to the corresponding methanodibenzo[*b*,*f*]diazocine **8** (Scheme 2) in low to moderate yield.[12] This condensation afforded the hitherto inaccessible nitro analogue of Tröger's base. No trace of the corresponding cyclic imides could be detected.

Table 1. Reaction of **6a–j** with dicarboxylic acids **3a–c** to **7a–p** and subsequent reduction to **8a–o**

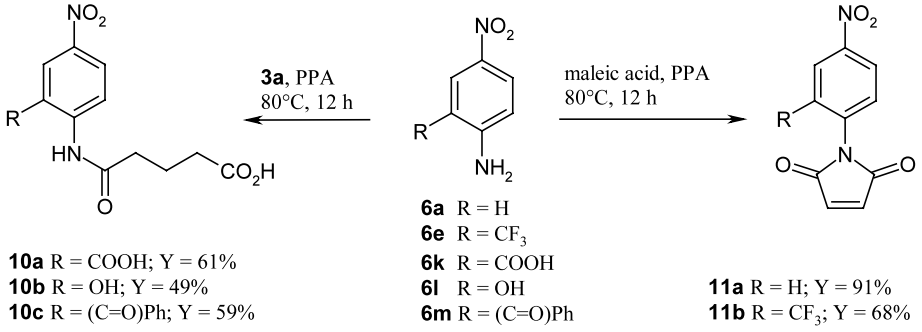


Entry	6	3	R	A	7	8	Yield[a] 7(8)%
1	**6a**	**3a**	H	CH_2	**7a**	**8a**	97(85)
2	**6a**	**3b**	H	bond	**7b**	**8b**	91(75)
3	**6a**	**3c**	H	$C(Me)_2$	**7c**	**8c**	98(71)
4	**6b**	**3b**	2-Cl	Bond	**7d**	**8d**	89(83)
5	**6c**	**3b**	2-Me	Bond	**7e**	**8e**	93(57)
6	**6d**	**3b**	2-OMe	Bond	**7f**	**8f**	89(95)
7	**6e**	**3b**	2-CF_3	Bond	**7g**	**8g**	97(70)
8	**6f**	**3b**	3-CF_3	Bond	**7h**	**8h**	93(58)
9	**6g**	**3b**	2-NO_2	Bond	**7i**	**8i**[b]	92(48[b])
10	**6h**	**3b**	2,3-diCl	Bond	**7j**	**8j**	91(86)
11	**6i**	**3b**	2-Ph	Bond	**7k**	**8k**	89(59)
12	**6j**	**3a**	2-Br	CH_2	**7l**	–	95(–)
13	**6c**	**3a**	2-Me	CH_2	**7m**	**8l**	98(93)
14	**6d**	**3a**	2-OMe	CH_2	**7n**	**8m**	97(84)
15	**6e**	**3a**	2-CF_3	CH_2	**7o**	**8n**	98(90)
16	**6f**	**3a**	3-CF_3	CH_2	**7p**	**8o**	95(85)

[a] Isolated yield; structures were confirmed by ^{1}H NMR as well as HRMS or elemental analyses.
[b] R = 2-NH_2.



Scheme 2. Reaction of compound **6a** with diglycolic acid **3d** and iminodiacetic acid **3e** to analogue **8** of Tröger's base.



Scheme 3. Reaction of amines **6k–m** with glutaric acid **3a** to the open chain acids **10a–c** and amines **6a** and **6e** with maleic acid to pyrrolediones **11a** and **11b**.

We next expanded this cyclocondensation to maleic acid (Scheme 3). Starting from anilines **6a** and **6e** the preparation of maleimides **11a** and **11b** proceeded in good to moderate yields, respectively.

A different course of reaction was observed for aniline substrates **6k–m** with a hydroxy-, carboxy- or benzoyl substituent at the 2 position (Scheme 3). In these cases the intermediate monoamides **10a–c** were formed as the sole products in moderate yields. The outcome of this reaction can be better ascribed to electronic effects than to steric factors.

Having obtained this overall encouraging result, we investigated the conversion of glutaric acid **3a** with other aniline substrates. We screened a variety of nitro, chloro, cyano and ethylanilines under standard conditions and examined the crude product by HPLC MS. 2-Nitro-, 3-nitro-, 4-ethyl-, 3-chloro- and 4-chloroanilines were transformed into the corresponding cyclic imides in 38–78% yield. The products of 2-ethyl, 3-ethyl, 2-chloroanilines and the parent aniline contained a mixture of the intermediate monoamides and the cyclic imides and the reaction of the aminobenzonitriles afforded a mixture of undefined products.

The nitro group of a variety of succinimides or glutarimides **7a–k,m–p** in Table 1 was reduced to the corresponding anilines **8a–o**, respectively, under hydrogenation conditions in good to excellent yield.[13] In the case of dinitro derivative **7i**, both groups were converted to the amine to give compound **8i** in moderate yield. In general, this reduction led to the starting materials (R = H, Fig. 1) for the synthesis of factor Xa inhibitors of type **1b**.

In summary, we have developed a novel, facile methodology for the one step synthesis of 4-nitroaryl substituted cyclic imides in high purity and yield. However, application to other aryl and heteroaryl compounds has to be confirmed. The subsequent reduction to the corresponding anilines offers an easy entry into the design of factor Xa inhibitors bearing a cyclic imide in the S4 pocket. The results of this investigation will be reported in due course.

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10. Representative experimental procedure: A mixture of 4-nitro-phenylamine **6a** (1.0 g, 7.2 mmol), glutaric acid **3a** (0.951 g, 7.2 mmol) and 86% polyphosphoric acid (10 g)

was heated at 80°C for 12 h. After cooling, water (50 ml) was added, the precipitate was filtered off and dried which afforded the 1-(4-nitro-phenyl)-piperidine-2,6-dione **7a** (1.63 g, 97%) as a colorless solid: mp 205–207°C; ^{1}H NMR (DMSO-d_6) δ 8.30 (d, $J=9.0$ Hz, 2H), 7.47 (d, $J=9.0$ Hz, 2H), 2.74 (t, $J=6.5$ Hz, 4H), 2.09–1.95 (m, 2H); MS (EI) m/z 234 (63, M^+), 206 (100). Anal. calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.46; H, 4.36; N, 12.16.

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12. For the synthesis of other analogues of Tröger's base, see: Jensen, J.; Wärnmark, K. *Synthesis* **2001**, 1873. Cf. spectral data of Tröger's base analogue **8**: mp 258–260°C; ^{1}H NMR (DMSO-d_6) δ 8.01 (dd, $J=6.2$ and $J=2.6$ Hz, 2H), 7.96 (d, $J=2.6$ Hz, 2H), 7.37 (d, $J=8.8$ Hz, 2H), 4.82 (d, $J=17.2$ Hz, 2H), 4.45 (d, $J=17.2$ Hz, 2H), 4.36 (s, 2H); MS (EI) m/z 312 (100, M^+). Anal. calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.50; H, 4.00; N, 17.90.
13. Representative experimental procedure: A mixture of 1-(4-nitro-phenyl)-piperidine-2,6-dione **7a** (1.0 g, 4.3 mmol), Raney Ni (0.1 g), and tetrahydrofuran (10 ml) was stirred at ambient temperature under hydrogen (1 atm) for 2 h. The reaction mixture was filtered through Celite, and the solvent was removed under vacuum to furnish 1-(4-amino-phenyl)-piperidine-2,6-dione **8a** (0.74 g, 85%) as a colorless solid: mp 214–216°C; ^{1}H NMR (DMSO-d_6) δ 6.67 (d, $J=8.7$ Hz, 2H), 6.53 (d, $J=8.7$ Hz, 2H), 5.11 (s, 2H), 2.67 (t, $J=6.5$ Hz, 4H), 2.0–1.86 (m, 2H); MS (EI) m/z 204 (100, M^+). Anal. calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.50; H, 6.00; N, 13.85.