Pergamon

Tetrahedron Letters 39 (1998) 8263–8266

TETRAHEDRON LETTERS

Solid-phase synthesis of pyrroles from enaminones and nitroalkenes

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Received 4 August 1998; accepted 4 September 1998

Abstract:
A versatile solid-phase synthesis of pyrrole-3-carboxamides from enaminones and α-alkyl-α-nitroalkenes is presented. The reaction is performed either in a two or three component pathway by treating a polymer bound enaminone with a nitroalkene or an aldehyde and a nitroalkane respectively.

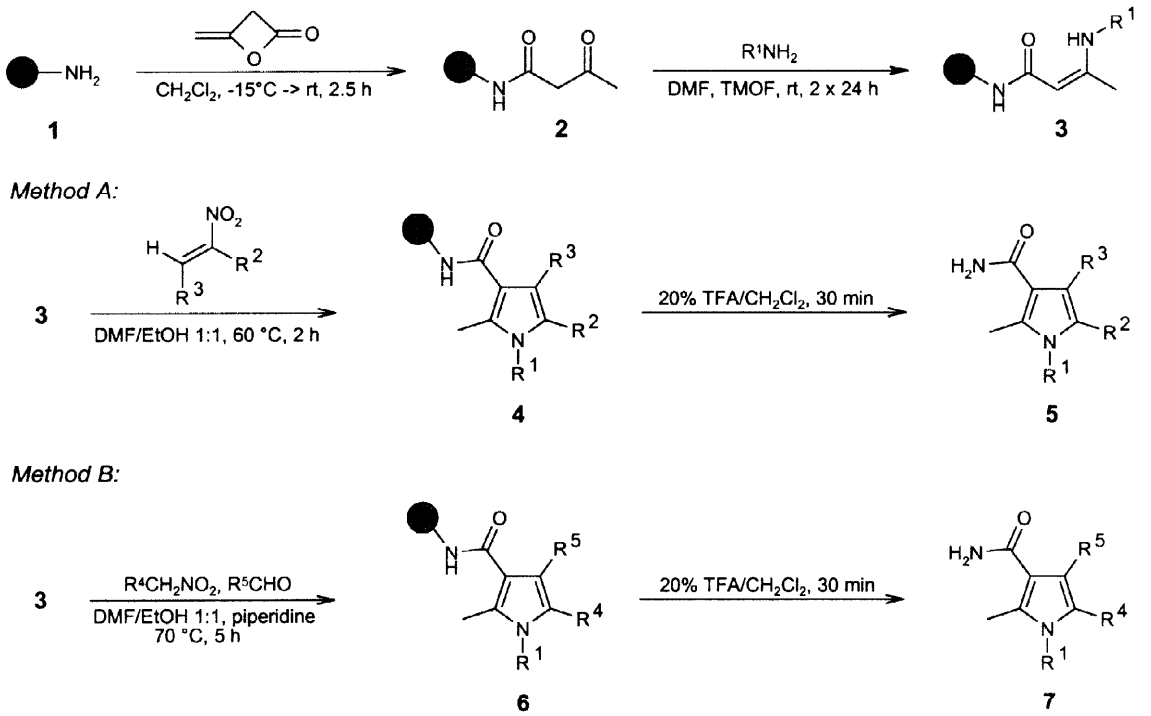
Keywords: *Pyrroles; Nitro compounds; Solid-phase synthesis; Combinatorial chemistry*

Combinatorial chemistry [1] has become a major tool in medicinal chemistry and solid-phase synthesis is by far the mostly applied technique for preparing small organic molecule libraries. Therefore there is a great need for developing new synthetic procedures on solid support. Among the most important and promising reactions are heterocyclic syntheses [2] and multicomponent reactions.[3]

Here we present a versatile solid-phase pyrrole synthesis [4] from nitroalkenes and enaminones. The mechanism of this reaction includes the Michael addition of the enaminone to the nitroalkene followed by an intramolecular Nef reaction under formation of the pyrrole ring.[5,6] As this reaction can be performed not only as a two component condensation but also in a three or four component pathway, it is ideally suited for the combinatorial synthesis of pyrrole libraries. The building blocks for the three component reaction can for example be an aldehyde, a nitroalkane and an enaminone while in the four component version an aldehyde, a nitroalkane, an amine and a β-ketoester or β-ketoamide are used.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01887-5

In the first step Rink Amide PS resin was acetoacetylated with diketene and converted into polymer bound enaminones **3** upon treatment with primary amines (Scheme 1).[7] The reaction conditions for the subsequent cyclization with nitroalkenes were then evaluated by using 2-phenylethylamine and 1-phenyl-2-nitroprop-1-ene. Optimal parameters for the synthesis of pyrroles **4** were: DMF/EtOH 1:1, 60 °C for 2 h. Highly pure pyrrole-3-carboxamides **5** were obtained after cleavage with 20% TFA/DCM (*Method A* in Scheme 1).[8]



Scheme1. Solid-phase synthesis of pyrroles from enaminones and nitroalkenes via a two (*Method A*) or three component pathway (*Method B*)

Table 1 shows some representative results of the two component strategy by using different amines and nitroalkenes. It turned out that α-alkyl substitution of the nitroalkene is necessary in order to obtain satisfying results as the α-H substituted 1-phenyl-2-nitroethene (entry 2 in Table 1) gave a complex product mixture under these reaction conditions. Attempts to optimize the conditions for this type of nitroalkene were not successful which may be due to the fact that these substrates are susceptible to polymerisation.

After having established the two component pathway on the solid phase we attempted to perform a three component condensation of the polymer bound enaminone with an aldehyde and a primary nitroalkane in order to increase the diversity of this reaction since only a limited number of α-alkyl-α-nitroalkenes for the two component strategy is commercially available.

Table 1
Representative results of the two component reaction

Entry	Amine	Nitroalkene	Yield[a]	Purity[b]
1	2-phenylethylamine	1-nitro-1-cyclohexene	85%	92%
2	2-phenylethylamine	1-phenyl-2-nitroethene	-	< 10%
3	2-(3,4-dimethoxyphenyl)ethylamine	1-(4-chlorophenyl)-2-nitroprop-1-ene	78%	96%
4	piperonylamine	1-(4-bromothienyl)-2-nitroprop-1-ene	52%	90%
5	cyclopropylamine	1-(4-chlorophenyl)-2-nitroprop-1-ene	75%	94%
6	2-furfurylamine	1-phenyl-2-nitroprop-1-ene	46%	90%
7	thiophene-2-ethylamine	1-(4-methoxyphenyl)-2-nitroprop-1-ene	69%	93%
8	tyramine	1-phenyl-2-nitroprop-1-ene	90%	95%
9	3-aminopropanol-1	1-(3-methoxyphenyl)-2-nitroprop-1-ene	89%	91%
10	2-(2-aminoethyl)pyridine	1-nitro-1-cyclohexene	84%	86%
11	N-(2-aminoethyl)morpholine	1-(3,4-methylendioxyphenyl)-2-nitro-prop-1-ene	79%	91%

[a] yield of the crude products based on the initial loading of the resin [b] determined by C18 RP HPLC at 214 nm

The three component reaction (*Method B* in Scheme 1) was carried out in DMF/EtOH 1:1 at 70 °C for 5 h with an aromatic aldehyde, a nitroalkane and piperidine as catalyst for the Henry reaction [9] which leads to the in situ formation of the nitroalkene.[8] Table 2 shows representative results of this reaction providing pyrrole-3-carboxamides **7**. The reaction works well with electron poor (entries 1,2,3,7,11), electron rich (entry 6) and hydroxy substituted (entry 5) aromatic aldehydes and several nitroalkanes except 2-nitroethanol (entry 4) which did not give the desired product under these reaction conditions.

Table 2
Representative results of the three component reaction

Entry	Amine	Aldehyde	Nitroalkane	Yield[a]	Purity[b]
1	2-phenylethylamine	4-trifluoromethylbenzaldehyde	nitroethane	75%	94%
2	2-phenylethylamine	4-trifluoromethylbenzaldehyde	1-nitropropane	63%	88%
3	2-phenylethylamine	4-trifluoromethylbenzaldehyde	methyl 4-nitrobutyrate	50%	91%
4	2-phenylethylamine	4-trifluoromethylbenzaldehyde	2-nitroethanol	-	0%
5	2-(3,4-dimethoxyphenyl)-ethylamine	3-hydroxybenzaldehyde	nitroethane	84%	90%
6	piperonylamine	3,4,5-trimethoxybenzaldehyde	nitroethane	60%	87%
7	cyclopropylamine	4-nitrobenzaldehyde	nitroethane	74%	90%
8	2-furfurylamine	4-fluorobenzaldehyde	nitroethane	88%	70%
9	tyramine	2-chlorobenzaldehyde	nitroethane	61%	81%
10	3-aminopropanol-1	4-chlorobenzaldehyde	nitroethane	89%	84%
11	2-(2-aminoethyl)pyridine	4-nitrobenzaldehyde	methyl 4-nitrobutyrate	66%	86%

[a] yield of the crude products based on the initial loading of the resin [b] determined by C 18 RP HPLC at 214 nm

In summary we have presented a versatile pyrrole synthesis from polymer bound enaminones and α-alkyl-α-nitroalkenes which was performed as a two or three component condensation. This synthesis should also be possible as a four component condensation or by attaching other components than the β-ketoamide to the solid phase, e. g. the aldehyde or the amine. It is therefore very useful for combinatorial chemistry and allows the generation of large pyrrole libraries.

Acknowledgements: This work was supported by the BMBF grant 03D0037A7.

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[8] *Typical procedure*: Rink Amide AM PS (1% DVB) resin (50 mg, capacity: 0.57 mmol/g) is suspended in DMF/piperidine 1:1 (500 µL) and shaken for 45 min. The resin is washed with DMF and this step is repeated once. The resin is suspended in DCM (500 µL) and a solution of diketene (15 µL) in DCM (250 µL) is added at 0 °C. After stirring for 30 min at 0 °C and 2 h at room temperature the resin is washed and suspended in DMF (600 µL). Trimethylorthoformate (62 µL) and 2-phenylethylamine (36 µL) are added. After 24 h at room temperature, the resin is washed with DMF and this step is repeated once. *Method A:* The resin is then suspended in DMF/EtOH 1:1 (1000 µL) and 1-phenyl-2-nitro-prop-1-ene (23 mg) is added. After stirring for 2 h at 60 °C the resin is washed and cleavage is performed with 20% TFA in DCM for 30 min. The solution is concentrated to dryness to provide the crude pyrrole which is then lyophilized from *tert*-butyl alcohol/water (4:1). *Method B:*The resin is suspended in DMF/EtOH 1:1 (1000 µL) and 4-trifluoromethylbenzaldehyde (19 µL), nitroethane (31 µL), piperidine (14 µL) and trimethylorthoformate (16 µL) are added. After stirring for 5 h at 70 °C the resin is washed and cleavage is performed with 20% TFA in DCM for 30 min. The solution is concentrated to dryness to provide the crude pyrrole which is then lyophilized from *tert*-butyl alcohol/water (4:1).
NMR data for entry 5 (Table 1): ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.89 (m, 2H), 1.08 (m, 2H), 2.16 (s, 3H), 2.40 (s, 3H), 2.99 (m, 1H), 7.20 (d, 2H), 7.56 (d, 2H); ^{13}C NMR (DMSO-d_6): δ 7.5, 11.2, 11.8, 25.7, 115.6, 117.8, 126.8, 127.8, 130.3, 131.1, 131.4, 134.9, 167.5.
NMR data for entry 7 (Table 2): ^{1}H NMR (DMSO-d_6, 250 MHz): δ 0.92 (m, 2H), 1.11 (m, 2H), 2.25 (s, 3H), 2.39 (s, 3H), 3.04 (m, 1H), 7.42 (d, 2H), 8.19 (d, 2H); ^{13}C NMR (DMSO-d_6): δ 7.6, 11.5, 11.8, 25.9, 116.1, 117.5, 123.0, 128.4, 130.1, 131.2, 143.5, 144.8, 167.4.

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