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Synthesis of nitrogen bicyclic scaffolds: pyrimido[1,2-*a*]pyrimidine-2,6-diones

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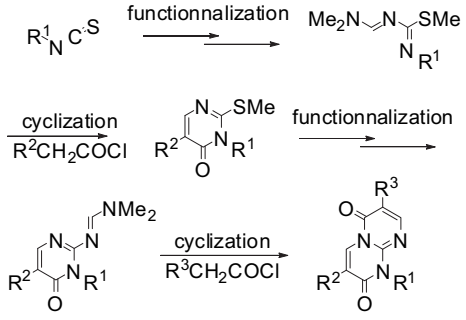
ABSTRACT

The multi-step synthesis of 1,3,7-trisubstituted pyrimido[1,2-*a*]pyrimidinediones starting from isothiocyanates is described. These nitrogen bicycles were prepared by an iterative sequence of functionalization/cyclocondensation reactions. [4+2] Cycloaddition reactions took place between diazadienic chains and various acyl chlorides providing sophisticated heterobicycles.

1. Introduction

Pyrimidopyrimidine moieties are widely represented both in natural and synthetic compounds, and usually display a broad range of biological properties.[1–3] Surprisingly, literature on general access to [1,2-*a*]-analogues—in which one of the three nitrogen atoms is at the junction of the two cycles—is rather limited, with the exception of some examples of specific one-pot or microwave assisted reactions.[4–7] In addition to the potential therapeutic applications, the pyrimido[1,2-*a*]pyrimidine compounds containing a guanidine-like moiety in the structure are also studied as ligands for catalytic activities.[8–10]

In this paper we describe an original and general method for the synthesis of pyrimido[1,2-*a*]pyrimidine-2,6-diones with an isothiocyanate starting material. Both heterocycles of the bicyclic structure are obtained through a cyclocondensation reaction between a diazadiene moiety and an acyl chloride. The synthesis is based on an iterative sequence (diazadiene formation followed by cyclization reaction) and consists of four parts (Scheme 1): functionalization of an isothiocyanate into a diazadienic chain; first cycloaddition reaction providing a pyrimidinone; introduction of a second diazadienic chain onto the structure; and second cycloaddition reaction providing a pyrimidopyrimidinedione.



Scheme 1.

2. Results and discussion

2.1. Pyrimidinone synthesis

The first step of the synthesis involved the conversion of commercially available isothiocyanates into the corresponding thioureas **1**. Reactions were performed in a solution of ammonia in methanol (7 M) in a sealed tube affording thioureas **1**, which then reacted with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in dichloromethane to give thiazadienes **2**. The thiocarbonyl groups were then alkylated with methyl iodide in tetrahydrofuran to afford 2-methylsulfanyl diazadienium iodides **3** in good yields (Scheme 2).

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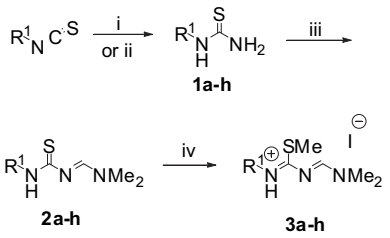


Scheme 2. Three-step synthesis of diazadienium iodides **3** from isothiocyanates. Reagents and conditions: (i) NH_3/MeOH 7 M (excess) for **1a**–**f** and **1h**; (ii) From benzoylisothiocyanate: *N*,*N*-dimethylhydrazine (1 equiv), EtOH, then HCl 4 M, H_2O for **1g**; (iii) DMFDMA (1.2 equiv), CH_2Cl_2; (iv) MeI (1.05 equiv), THF.

The three-step synthetic sequence from isothiocyanates to diazadienium iodides **3** proved to be attractive because of an easy work-up, short reaction times, scalability and high yields. For example 40 g of the compound **3b** (R^1=*p*Tol) was synthesized in one batch in 95% overall yield. Diazadienium iodides **3a**–**h** were obtained with excellent yields independent of the nature of the R^1 group (Table 1): hydrogen (entry 1), aryl (entries 2–4), alkyl (entries 5 and 6), electron donating group (entry 7), and electron withdrawing group (entry 8).[11–13] The compound **1g** (R^1=NMe_2, entry 7) was obtained by a different method in two steps through reaction of *N*,*N*-dimethylhydrazine with benzoylisothiocyanate followed by hydrolysis of the benzoyl group under acidic conditions.

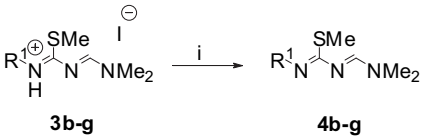
Table 1
Synthesis of thioureas **1**, thiazadienes **2**, diazadienium iodides **3**, and diazadienes **4** (Schemes 2 and 3)

Entry	R^1	Compd (**1**) (%)[a]	Compd (**2**) (%)[d]	Compd (**3**) (%)[e]	Compd (**4**) (%)[f]
1	H	**1a**[b]	**2a** (100)	**3a** (100)	**4a** (—)
2	*p*Tol	**1b** (98)	**2b** (99)	**3b** (100)	**4b** (96)
3	Ph	**1c**[b]	**2c** (94)	**3c** (98)	**4c** (98)
4	mCl_2Ph	**1d** (95)	**2d** (95)	**3d** (99)	**4d** (94)
5	Me	**1e**[b]	**2e** (98)	**3e** (98)	**4e** (76)
6	cHx	**1f** (95)	**2f** (95)	**3f** (98)	**4f** (88)
7	NMe_2	**1g** (68)[c]	**2g** (97)	**3g** (95)	**4g** (78)
8	Ac	**1h**[b]	**2h** (96)	**3h** (98)	**4h** (—)

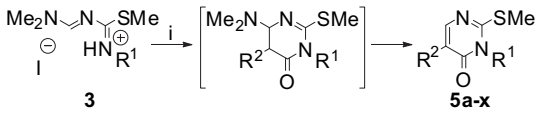
[a] Reagents and conditions: NH_3/MeOH (7 M).
[b] Commercially available.
[c] From benzoylisothiocyanate: *N*,*N*-dimethylhydrazine (1 equiv), EtOH, then HCl 4 M, H_2O.
[d] DMFDMA (1.2 equiv), CH_2Cl_2.
[e] MeI (1.05 equiv), THF.
[f] Saturated aqueous $NaHCO_3$, Et_2O.

A further neutralization step led to the formation of neutral diazadienic chain containing compounds **4b**–**g** (Scheme 3). The reaction was performed under basic conditions using aqueous $NaHCO_3$. However, diazabutadienes **4a** (R^1=H) and **4h** (R^1=Ac) were not obtained, and analogues **4b**–**g** showed rapid degradation. Conversely, all diazadienium salts **3a**–**h** were very stable and proved to be reactive in this ionic form.[13,14] Indeed, the first cyclization reaction took place between the diazadienium iodides **3** and acyl chlorides in basic medium to give pyrimidin-4(3*H*)-ones **5** (Scheme 4).[15] Intermediary cycloadducts were not isolated due to spontaneous loss of dimethylamine; the tandem [4+2] cycloaddition/deamination led to the formation of the expected pyrimidin-4(3*H*)-one together with a secondary product (a *N*,*N*-dimethylamide corresponding to the addition of dimethylamine onto the acyl chloride), but this was easily removed by aqueous wash.

Compounds **5a**–**x** were synthesized with moderate to excellent yields (Table 2). For compounds **5b** (R^1=*p*Tol, R^2=CF_3; entry 2) and **5g** (R^1=*p*Tol, R^2=NMe_2; entry 7), the acyl chlorides were not commercially available and were prepared from the corresponding carboxylic acids (1,1,1-trifluoropropionic acid for **5b**; *N*,*N*-dimethylglycine for **5g**). The poor solubility of *N*,*N*-dimethylglycine in common organic solvents is responsible for the dramatic decrease of yield (11%). For compound **5f** (entry 6), microwave irradiation activation[16] allowed us to improve the reaction yield from 65% to 95%. For compounds **5p**–**r** (R^1=Ac, entries 16–18) low yields were obtained due to partial deacetylation of the nitrogen atom.



Scheme 3. Synthesis of diazadienes **4**. Reagents and conditions: (i) saturated aqueous $NaHCO_3$, Et_2O.



Scheme 4. Synthesis of pyrimidin-4(3*H*)-ones **5** from diazadienium iodides **3**. Reagents and conditions: (i) R^2CH_2COCl (3 equiv), NEt_3 (4 equiv), CH_2Cl_2.

Table 2
Synthesis of *N*-substituted pyrimidinones **5** from diazadienium iodides **3** (Scheme 4)

Entry	R^1	R^2	Compd (**5**) (%)[a]
1	*p*Tol	CO_2Me	**5a** (97)
2	*p*Tol	CF_3	**5b** (97)[b]
3	*p*Tol	H	**5c** (95)
4	*p*Tol	Ph	**5d** (85)
5	*p*Tol	OMe	**5e** (90)
6	*p*Tol	Me	**5f** (95)[c]
7	*p*Tol	NMe_2	**5g** (11)[b]
8	Me	CO_2Me	**5h** (91)
9	Me	H	**5i** (86)
10	Me	Ph	**5j** (74)
11	Me	OMe	**5k** (62)
12	Me	Me	**5l** (73)
13	H	CO_2Me	**5m** (82)
14	H	H	**5n** (68)
15	H	Ph	**5o** (80)
16	Ac	CO_2Me	**5p** (37)
17	Ac	H	**5q** (47)
18	Ac	Ph	**5r** (10)
19	NMe_2	CO_2Me	**5s** (76)
20	NMe_2	H	**5t** (84)
21	NMe_2	Ph	**5u** (72)
22	mCl_2Ph	CO_2Me	**5v** (79)
23	mCl_2Ph	H	**5w** (78)
24	mCl_2Ph	Ph	**5x** (95)

[a] Reagents and conditions: R^2CH_2COCl (3 equiv), NEt_3 (4 equiv), CH_2Cl_2.
[b] $R^2CH_2CO_2H$ (3 equiv), $(COCl)_2$ (3.3 equiv), DMF (0.1 equiv), CH_2Cl_2, 0 °C; then **4b** (1.0 equiv), NEt_3 (4 equiv), CH_2Cl_2.
[c] Under microwave irradiation: 50 °C, 60 W, 15 min.

2.2. From pyrimidinone rings to bicyclic structures

At this point we chose to limit our study to the five compounds **5a**–**e** (R^1=*p*Tol) for the installation of the second ring. The *para*-tolyl group was chosen for two main reasons: this group gave the best general yields for the sequence from *para*-tolylisothiocyanate to pyrimidinones **5** (except for **5g**), and it showed a specific NMR signal (a singlet between 2.4 and 2.6 ppm), which was a practical tool to follow reaction progress.