Tetrahedron 68 (2012) 1011–1016

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Combination of hydrazine polyanion strategy and ring-closing metathesis in the synthesis of heterocycles

Svetlana Tšupova, Oleg Lebedev, Uno Mäeorg *

Institute of Chemistry, University of Tartu, Ravila 14a, 50411 Tartu, Estonia

ARTICLE INFO

Article history:
Received 22 September 2011
Received in revised form 5 November 2011
Accepted 28 November 2011
Available online 6 December 2011

Keywords:
Hydrazines
Heterocycles
Alkylation
Dianion
Ring-closing metathesis

ABSTRACT

An efficient method for the synthesis of cyclic hydrazine derivatives starting from disubstituted hydrazines is reported. The method is based on the selective alkylation of hydrazine dianions with bromoalkenes and subsequent cyclization using Grubbs' catalysts. The described method provides fast and easy access to the substrates for ring-closing metathesis and the corresponding heterocycles containing a hydrazine moiety. The scope and limitations of the new method are also demonstrated.

1. Introduction

Hydrazine derivatives are well-known compounds used as pesticides, dyes, drugs and building blocks in organic synthesis. Currently known hydrazine-based drugs are used for the treatment of tuberculosis, hypertension and Parkinson's disease.[1] Some hydrazines demonstrate neuroprotective properties and are used as antidepressants.[2] Also, hydrazine-based peptidomimetics were shown to be potent agents against hepatitis[3] and AIDS.[4] In recent years, great interest in the synthesis of heterocyclic hydrazine derivatives has emerged since certain compounds were proven to show remarkable biological activities.[5–7]

A number of methods for the synthesis of heterocycles containing endocyclic N–N bond have been developed. Mainly these compounds are prepared by direct alkylation of hydrazines with dihalides,[8–10] however, Diels–Alder[11,12] and Mitsunobu[13] transformations are also utilized. These methods are good for the synthesis of particular molecules, but the scope is limited to five-, six- and seven-membered rings. The scope may be significantly expanded by applying a ring-closing metathesis (RCM) strategy, however, it requires efficient methods for the synthesis of the corresponding dienes, which is an additional challenge. Synthesis of cyclic hydrazines by the RCM reaction was first mentioned by Tae.[14,15] At the same time, the problem of efficient synthesis of alkene-bearing hydrazines was not solved, which still hampers the development of effective hydrazine-based RCM platform.

In our current work we provide an efficient one-pot method for the synthesis of the corresponding dienes based on a hydrazine polyanion strategy, the advantages of which have been shown in our previous works.[16–19] The dienes were further converted to the corresponding heterocycles via the RCM reaction.

2. Results and discussion

We started with symmetrical dialkylation of dianions with bromoalkenes (Scheme 1). The dianions from PhNHNHBoc, EtNHNHBoc and BocNHNHBoc were generated by treatment with 2 equiv of BuLi in THF at −78 °C with subsequent addition of the alkylating agent. The reaction progress was monitored by TLC. The addition of 2 equiv of allyl bromide to the dianions lead to the rapid formation of the monoalkylated products (1 h) and the slow formation of the dialkylated products (1–3 days) even at 40 °C. At room temperature the reactions were incomplete. Unfortunately, we failed to introduce the alkenyl groups with longer chain in the similar manner obtaining the monoalkylated products with a small amount of the dialkylated species. We propose the different reasons for the alkylation reactions with 4-bromobutene and 5-bromopentene. The dianion being also a strong base may promote elimination of 4-bromobutene with formation of butadiene. We suppose the dialkylation with 5-bromopentene was incomplete because of steric problems as similar behaviour has been previously observed.[16]

* Corresponding author. Tel.: +372 7375243; fax: +372 7375264; e-mail address: uno@chem.ut.ee (U. Mäeorg).

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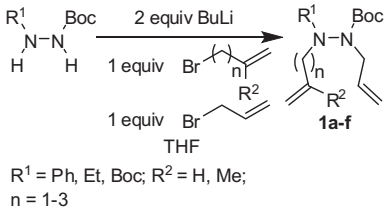
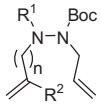
doi:10.1016/j.tet.2011.11.091



Scheme 1. Direct dialkylation of dianions.

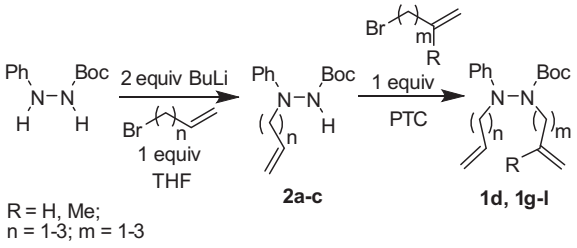
Considering these limitations next we tried the consecutive one-pot monoalkylation of both nitrogens of the PhNHNHBoc dianion to introduce the alkenyl groups with longer or branched chain onto the Ph nitrogen and smaller allyl group onto the Boc nitrogen (Scheme 1). The corresponding products were obtained in good yields (Table 1). Again, the formation of the dialkylated products took 1–2 days at 40 °C.

Table 1
Products of direct alkylation of dianions



	R^1	R^2	*n*	Conditions	Yield, %
1a[16]	Ph	H	1	2 equiv of AllBr, −78 °C to 40 °C, 1 day	77
1b	Et	H	1	2 equiv of AllBr, −78 °C to 40 °C, 1 day	49
1c[20]	Boc	H	1	2 equiv of AllBr, −78 °C to 40 °C, 3 days	81
1d	Ph	H	2	CH_2=$CH(CH_2)_2$Br, −78 °C, 1 h; AllBr, 40 °C, 2 days	60
1e	Ph	H	3	CH_2=$CH(CH_2)_3$Br, −78 °C, 1 h; AllBr, 40 °C, 2 days	81
1f	Ph	Me	1	CH_2=$C(CH_3)CH_2$Br, −78 °C, 1 h; AllBr, 40 °C, 1 day	80

To synthesize the dienes containing substituents with a longer chain on the Boc nitrogen we worked out another methodology. At first we performed monoalkylation of the PhNHNHBoc dianion with 1 equiv of the alkylating agent. The monoalkylated derivatives formed within 1 h and were obtained in very good yields. Further alkylation was performed under PTC conditions (K_2CO_3/NaOH/TBAHS/toluene) at room temperature (Scheme 2).

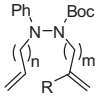


Scheme 2. Monoalkylation of dianions and further alkylation under PTC conditions.

Generally 1 equiv of the alkylating agent was used and the reaction was complete after 1 day. However, in some cases (entries **1j** and **1l**) 2 equiv of 4-bromobutene and longer reaction times were required. The corresponding dienes were obtained in good or excellent yields (Table 2). As both alkylation reactions were very clean we decided to make this approach easier and to perform the same reaction sequence in a one-pot fashion without separation of the monoalkylated product. We found that such way has the same efficiency and may be successfully used (entry **1k**). To the best of our knowledge, this one-pot method for the synthesis of alkene-bearing hydrazines has not been previously reported.

RCM studies started with the cyclization of **1a** using Grubbs' first generation catalyst (Scheme 3). We found that the use of 5 mol % of the catalyst seemed to be optimal for the cyclization. For example,

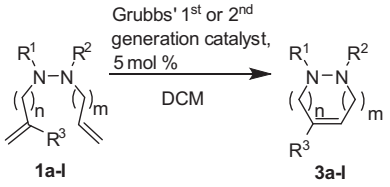
Table 2
Products of mono- and double alkylation



R		*n*	*m*	Conditions	Yield, %
2a[16]		1		AllBr, −78 °C, 1 h;	90
2b		2		CH_2=$CH(CH_2)_2$Br, −78 °C, 1 h	80
2c		3		CH_2=$CH(CH_2)_3$Br, −78 °C, 1 h	75
1d	H	2	1	1 equiv AllBr, rt, 1day	81[a]
1g	H	1	2	1 equiv CH_2=$CH(CH_2)_2$Br, rt, 1 day	93[a]
1h	H	1	3	1 equiv CH_2=$CH(CH_2)_3$Br, rt, 1 day	91[a]
1i	Me	1	1	1 equiv CH_2=$C(CH_3)CH_2$Br, rt, 1 day	61[a]
1j	H	2	2	2 equiv CH_2=$CH(CH_2)_2$Br, rt, 2 days	71[a]
1k	H	2	3	1 equiv CH_2=$CH(CH_2)_2$Br, rt, 1 day	79[a]
1k	H	2	3	1 equiv CH_2=$CH(CH_2)_2$Br, −78 °C, 1 h; 1 equiv CH_2=$CH(CH_2)_3$Br, rt, 1 day	65[b]
1l	H	3	2	2 equiv CH_2=$CH(CH_2)_2$Br, rt, 2 days	71[a]

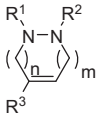
[a] Synthesized from the corresponding monoalkylated derivative.
[b] One-pot synthesis starting from PhNHNHBoc.

using 2 and 5 mol % of the catalyst the corresponding six-membered ring **3a** was obtained in 39% and 89% yields, respectively. All other dienes containing unsubstituted double bonds except **1b** were cyclized under the same conditions (Table 3). Compound **1b** did not react at all in the presence of Grubbs' first generation catalyst, so, the corresponding cycle was obtained by employing Grubbs' second generation catalyst. A possible reason for such behaviour is that **1b** may also act as a ligand interacting and deactivating the catalyst. The interaction with the second generation catalyst must be much weaker because of higher electron density on the Ru atom and hence the ring-closed product **3b** may be obtained. Prochiral cycles **3f** and **3i** were also synthesized utilizing Grubbs' second generation catalyst.



Scheme 3. Ring-closing metathesis of dienes.

Table 3
Products of ring-closing metathesis



	R^1	R^2	R^3	*n*	*m*	Conditions	Yield, %
3a	Ph	Boc	H	1	1	GI, 5 mol %, rt, 30 min[a]	89
3b	Et	Boc	H	1	1	GII, 5 mol %, rt, 1 day[b]	71
3c[21]	Boc	Boc	H	1	1	GI, 5 mol %, rt, 2 h[a]	87
3d	Ph	Boc	H	2	1	GI, 5 mol %, rt, 1 day[a]	88
3e	Ph	Boc	H	3	1	GI, 5 mol %, rt, 1 day[a]	94
3f	Ph	Boc	Me	1	1	GII, 5 mol %, rt, 1 day[b]	80
3g	Ph	Boc	H	1	2	GI, 5 mol %, rt, 1 day[a]	86
3h	Ph	Boc	H	1	3	GI, 5 mol %, rt, 1 day[a]	81
3i	Boc	Ph	Me	1	1	GII, 5 mol %, rt, 1 day[b]	82
3j	Ph	Boc	H	2	2	GI, 5 mol %, rt, 2 h[a]	77
3k	Ph	Boc	H	2	3	GI, 5 mol %, rt, 1 day[a]	54
3l	Ph	Boc	H	3	2	GI, 5 mol %, rt, 1 day[a]	51

[a] GI=Grubbs' first generation catalyst.
[b] GII=Grubbs' second generation catalyst.