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Rapid generation of molecular complexity using 'sequenced' multi-component reactions: one-pot synthesis of 5,5′-disubstituted hydantoins from methyleneaziridines

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Abstract—2-Methyleneaziridines can be transformed into 5,5′-disubstituted hydantoins in moderate to good yield (48–75%) via a 'one-pot' process that brings together up to six components in an orchestrated way.
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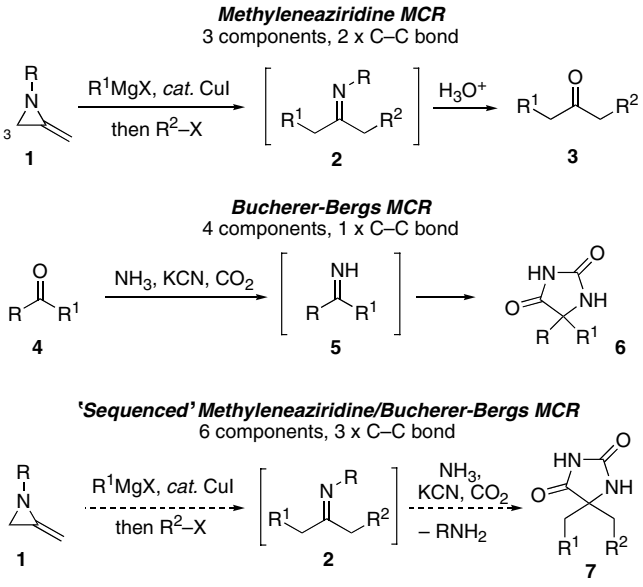
Multi-component reactions (MCRs) are one-pot processes in which three or more components come together to form a product containing substantial elements of all the reactants.[1,2] They provide an inherently more efficient approach to chemical synthesis than conventional bimolecular reactions, and considerable current effort is focused on the development of new MCRs.[3] Recently, a powerful new example based upon the highly strained methyleneaziridine ring system has been developed in our laboratory (Scheme 1).[4,5] This MCR[6] involves ring opening of methyleneaziridine **1** at C-3 using a Grignard reagent under Cu(I) catalysis, and capture of the resultant metalloenamine with a carbon based electrophile (R^2–X). Simple hydrolysis of ketimine **2** provides a flexible method for the synthesis of 1,3-disubstituted propanones, for example, **3**. Good variation in the structure of all three components has been demonstrated,[4,5] and it can be performed either in solution,[4] or in solid phase.[5]

Hydantoins are important heterocyclic scaffolds that induce prominent biological effects.[7] Additionally, they serve as useful precursors to non-natural amino acids via chemical[7] or enzymatic hydrolysis.[8] These heterocycles are often made by the Bucherer–Bergs reaction which converts an aldehyde (or ketone) into the corresponding hydantoin **6** via a 4-component reaction involving NH imine **5** (Scheme 1).[9,10] Despite the utility of this reaction, it is limited by the fact that only changes in the structure of **4** lead to variation in the structure of the final hydantoin (i.e., just one point of chemical diversity). Thus, for every hydantoin to be synthesised, the appropriate ketone has to be purchased or prepared. To extend the use of this MCR in drug discovery programmes, it would be desirable if the number of points of chemical diversity could be increased.[11]



Scheme 1. Rationale behind new MCR approach to hydantoins.

Keywords: Aziridines; Nitrogen heterocycles; Molecular diversity; Multi-component reactions; Strained compounds.
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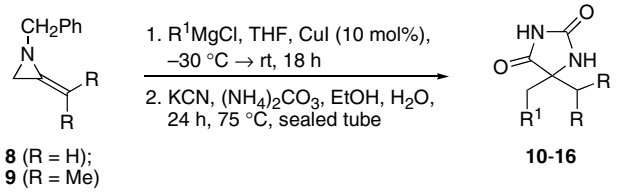
We reasoned that a 'sequenced' process combining elements of the methyleneaziridine and Bucherer–Bergs MCRs might provide a very rapid and flexible approach to 5,5′-disubstituted hydantoins (Scheme 1). Thus, after initial ring opening and alkylation of **1**, introduction of carbon dioxide, ammonia and potassium cyanide to the vessel might lead directly to the formation of **7** by way of a 6-component reaction (6-CR) that produces three new intermolecular C–C bonds. By systematic variation in the structure of the aziridine, organometallic reagent and the electrophile, three points of chemical diversity can be generated. In this letter, we demonstrate that a range of 5,5′-disubstituted hydantoins can be made in moderate to good yields using this strategy.

1-Benzyl-2-methyleneaziridine (**8**)[12] and 1-benzyl-2-isopropylidineneaziridine (**9**)[13] used in this study were readily made in two steps from 2,3-dibromopropene and 1,1-dibromo-2,2-dimethylcyclopropane, respectively. Initial studies focused on simpler 5-component reactions (5-CRs) wherein the metalloenamine alkylation step was omitted. Encouragingly, treatment of **8** with ^{n}BuMgCl (2.0 equiv) and CuI (10 mol %) in THF for 18 h followed by addition of EtOH, KCN, $(NH_4)_2CO_3$ and H_2O and subsequent heating at 75 °C produced crystalline hydantoin **10** in 71% overall yield after aqueous work up and recrystallisation (Scheme 2 and Table 1, entry 1). Since it proved necessary to conduct the Bucherer–Bergs step in a closed system to obtain high yields, an ACE® pressure tube was used as the vessel for the entire reaction sequence. Moreover, good yields were obtained with a range of simple Grignard reagents using either **8** or **9** as the aziridine component (Table 1, entries 2–7).

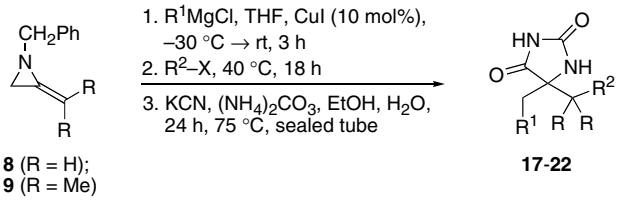


Scheme 2. Hydantoin synthesis by 'one-pot' 5-CR.

Table 1. Examples of 'one-pot' 5-component hydantoin synthesis

Entry	Aziridine	R	Grignard	Hydantoin	Yield[a] (%)
1	**8**	H	^{n}BuMgCl	**10**	71
2	**8**	H	$PhCH_2MgCl$	**11**	71
3	**8**	H	EtMgCl	**12**	54
4	**8**	H	AllylMgCl	**13**	51
5	**8**	H	^{i}BuMgCl	**14**	73
6	**9**	Me	$PhCH_2MgCl$	**15**	75
7	**9**	Me	^{i}BuMgCl	**16**	72

[a] Isolated yield after aqueous work-up and recrystallisation. Detailed experimental procedure provided in the Supplementary data.



Scheme 3. Hydantoin synthesis by 'one-pot' 6-CR.

A second series of experiments were undertaken in which alkylation of the metalloenamine was undertaken prior to hydantoin formation. Thus, treatment of **8** with ^{n}BuMgCl (2.0 equiv) and CuI (10 mol %) in THF for 3 h, then benzyl chloride (1.5 equiv) for 18 h at 40 °C and finally EtOH, KCN, $(NH_4)_2CO_3$ and H_2O at 75 °C produced crystalline hydantoin **17** in 69% overall yield after crystallisation (Scheme 3 and Table 2, entry 1). The scope of this 6-CR has been further tested by variation in the nature of the Grignard reagent, electrophile and aziridine components (Table 2, entries 2–6). Whilst the chemical yields obtained in some instances are modest, the efficiency is very good when viewed in the context of the total number of new bonds made (3 × C–C; 4 × C–N bonds). The tolerance of these new 5- and 6-CRs with respect to changes in the structure of the methyleneaziridine, Grignard and electrophile appears broadly in line with the original ketone MCR.[4c] Using aziridine **9**, only products derived from nucleophilic attack at C-3 were isolated, an outcome consistent with other MCRs involving this type of substrate.[4,5]

To conclude, a simple 6-CR for the assembly of 5,5′-disubstituted hydantoins involving 3-points of chemical diversity has been established. Work to develop this and other MCRs is ongoing in our laboratory.

Acknowledgements

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Table 2. Examples of 6-component hydantoin synthesis from methyleneaziridines

Entry	Aziridine	R	Grignard	R^2–X	Hydantoin	Yield[a] (%)
1	**8**	H	^{n}BuMgCl	$PhCH_2Cl$	**17**	69
2	**8**	H	^{n}BuMgCl	p-$BrC_6H_4CH_2Br$	**18**	71
3	**8**	H	$PhCH_2MgCl$	p-$BrC_6H_4CH_2Br$	**19**	66
4	**9**	Me	EtMgCl	p-$MeOC_6H_4CH_2Cl$	**20**	56
5	**9**	Me	$PhCH_2MgCl$	MeI	**21**	48
6	**9**	Me	^{i}BuMgCl	$PhCH_2Br$	**22**	69

[a] Isolated yield after aqueous work-up and recrystallisation. Detailed experimental procedure provided in the Supplementary data.

Service Centre for performing some of the mass measurements.

Supplementary data

The Supplementary data includes general procedures for the synthesis of **10**–**22** and full characterisation data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.135.

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