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Solid-Phase, Multicomponent Reactions of Methyleneaziridines: Synthesis of 1,3-Disubstituted Propanones

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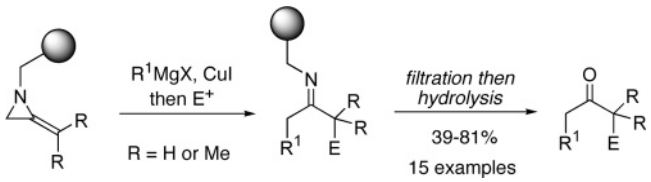
ABSTRACT



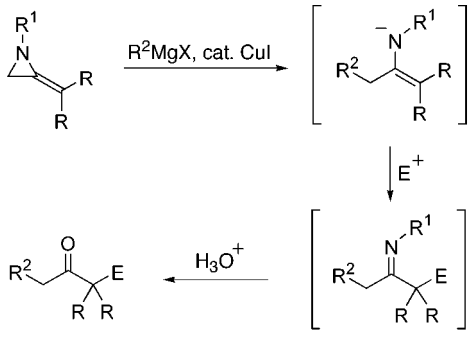
Polymer-supported methyleneaziridines undergo ring opening by Grignard reagents under copper catalysis to yield metalloenamines which are alkylated in situ to yield ketimines. Filtration and washing of these Merrifield resin-bound intermediates prior to hydrolysis provides the corresponding 1,3-disubstituted propanones in a high state of purity without recourse to column chromatography.

Organic molecules are traditionally made by executing a sequence of chemical reactions, which forge the union of two components in each step. In this way, the complexity of a target molecule is built up by a linear sequence of transformations. An increasingly popular and intrinsically more efficient approach to chemical synthesis centers around the use of multicomponent and related processes which bring together three or more components in an orchestrated way in a single reaction vessel.[1,2]

Recently, we reported a new and quite general multicomponent reaction (MCR) based upon the highly strained methyleneaziridine ring system.[3−6] Using Grignard reagents as the nucleophilic component and a range of different electrophiles, a variety of 1,3-disubstituted propanones could be produced in one-pot using the chemistry depicted in Scheme 1.[4] By reducing rather than hydrolyzing the intermediate ketimine, amines[5] and *N*-heterocycles[6] were produced using the same general approach.

The methyleneaziridine-based MCR has a number of attributes which make it quite attractive: (i) two new intermolecular C−C bonds are produced; (ii) the initially formed ketimines are extremely versatile synthetic intermedi-

Scheme 1. Ketone Synthesis Using Aziridine MCR



where E^+ = alkyl halide or tosylate, epoxide, ArCHO, etc
R = H or alkyl

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(1) For reviews, see: (a) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169. (c) Weber, L. *Drug Discovery Today* **2002**, *7*, 143. (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (e) Hulme, C.; Nixey, T. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 921. (f) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (g) Syamala, M. *Org. Prep. Proc. Int.* **2005**, *37*, 103.

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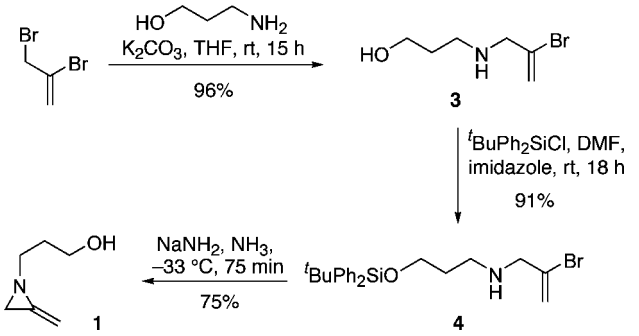
ates; (iii) it is operationally simple with the methyleneaziridine starting materials accessible in 2−3 chemical steps and many Grignard reagents and electrophiles commercially available; (iv) asymmetric variants of this MCR have been demonstrated using chiral, nonracemic methyleneaziridines.[5,6] However, limitations do exist with this method. For example, we have witnessed competitive coupling of the Grignard reagent with the electrophile producing R^2−E under the reaction conditions.[4b] While this byproduct can usually be removed by chromatography, this is inconvenient and makes the chemistry rather unsuitable for the synthesis of compound libraries using high-throughput techniques. By attachment of the methyleneaziridine to a solid support via the nitrogen atom (i.e., R^1 = polymer support, Scheme 1), it was anticipated that this limitation could be overcome. After ring opening and alkylation, filtration and washing of the resin-bound ketimine prior to hydrolysis would remove excess reagents and solution byproducts (e.g., R^2−E), negating the need for chromatographic purification. The feasibility of performing this chemistry on solid-phase was supported by the work of Wipf and Henninger, who have demonstrated that alkenyl−aziridines attached to Wang resin undergo S_N2' opening using alkylcyanocuprates.[7]

A number of strategies can be imagined for the attachment of methyleneaziridines to polymer supports via the aziridine nitrogen atom. For simplicity, we focused on using an ether linkage because of the known tolerance of this functional group to the organometallic reagents required for the MCR. Thus, initial studies centered on the preparation of two hydroxyl-functionalized methyleneaziridines **1** and **2** suitable for attachment to halogenated polymers by means of the Williamson ether synthesis. The synthesis of methyleneaziridine **1** was achieved in three steps in 66% overall yield (Scheme 2). Alkylation of 2,3-dibromopropene with 3-aminopropanol yielded amino alcohol **3**, which was further protected as its *tert*-butyldiphenylsilyl ether. Ring closure of silyl ether **4** with sodium amide in liquid ammonia[8] yielded methyleneaziridine **1**, in which concomitant deprotection of the silyl ether was achieved. The use of shorter reaction times

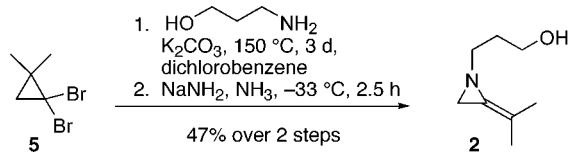
Scheme 2. Preparation of 2-Methyleneaziridine **1**



led to mixtures of **1** and its O-silylated counterpart, indicating that cyclization precedes deprotection. Unfortunately, direct ring closure of **3** ($NaNH_2$ (3.5 equiv), NH_3, −33 °C, 30 min) produced **1** and $HO(CH_2)_3NHCH_2C{\equiv}CH$ as an inseparable 12:88 mixture.

Aziridine **2** was made in two steps as depicted in Scheme 3. Ring opening of 1,1-dibromo-2,2-dimethylcyclopropane

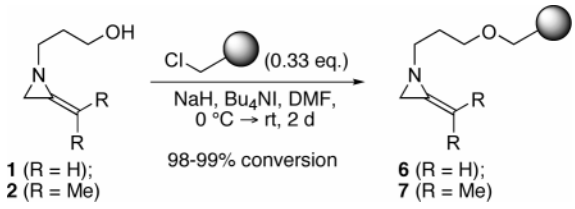
Scheme 3. Synthesis of 2-Isopropylidineaziridine **2**



5 with 3-aminopropanol yielded 3-(2-bromo-3-methylbut-2-enylamino)propan-1-ol,[9] which in this instance was successfully cyclized to **2** without recourse to O-protection.

Etherification of methyleneaziridines **1** and **2** with Merrifield resin (4.15 mmol/g) provided excellent yields of the resin-bound derivatives **6** and **7**, respectively (Scheme 4).[10]

Scheme 4. Assembly of Resin-Bound Methyleneaziridines



The supported methyleneaziridines were characterized by IR spectroscopy, ^{13}C gel-phase NMR spectroscopy (see Supporting Information),[11] and the resin loadings (2.85−3.12

(2) For recent illustrative examples, see: (a) Janvier, P.; Bois-Choussy, M.; Bienayme, H.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 811. (b) Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077. (c) Toure, B. B.; Hall, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 2001. (d) Knapton, D. J.; Meyer, T. Y. *J. Org. Chem.* **2005**, *70*, 785. (e) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 2836. (f) Tejedor, D.; Santos-Exposito, A.; Gonzalez-Cruz, D.; Marrero-Tellado, J. J.; Garcia-Tellado, F. *J. Org. Chem.* **2005**, *70*, 1042. (g) Dietrich, S. A.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2005**, *3*, 97. (h) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874.

(3) Since this process involves the reaction of two reagents together to form an intermediate that is captured by the subsequent addition of a further reagent, it is more precisely defined as a sequential component reaction; see ref 1f.

(4) (a) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2000**, 1791. (b) Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935.

(5) Hayes, J. F.; Shipman, M.; Slawin, A. M. Z.; Twin, H. *Heterocycles* **2002**, *58*, 243.

(6) Hayes, J. F.; Shipman, M.; Twin, H. *Chem. Commun.* **2001**, 1784.

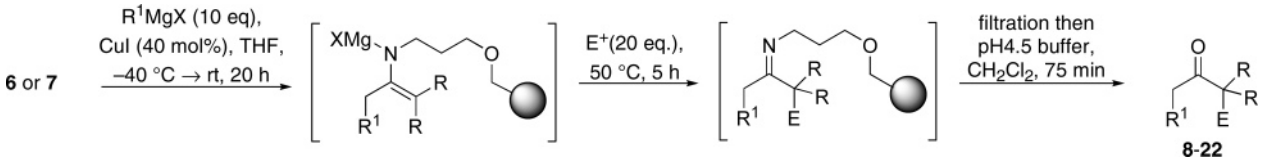
(7) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586.

(8) (a) Pollard, C. B.; Parcell, R. F. *J. Am. Chem. Soc.* **1951**, *73*, 2925. For the correct structural assignments, see: (b) Ettlinger, M. G.; Kennedy, F. *Chem. Ind.* **1956**, 166. (c) Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc.* **1957**, *79*, 1462.

(9) (a) Quast, H.; Risler, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 414. (b) Wijnberg, J. B. P. A.; Wiering, P. G.; Steinberg, H. *Synthesis* **1981**, 901. (c) Quast, H.; Jakob, R.; Peters, K.; Peters, E.-M.; von Schnering, H. G. *Chem. Ber.* **1984**, *117*, 840.

(10) Nam, N.-H.; Sardari, S.; Parang, K. *J. Comb. Chem.* **2003**, *5*, 479 and references therein.

Scheme 5. Solid-Phase Ketone Synthesis



mmol/g) and percentage conversions calculated using combustion analysis data.

With supported methyleneaziridines **6** and **7** in hand, we turned our attention to the solid-phase MCR. Under optimized conditions, **6** was converted into 1-phenyloctan-3-one (**8**) in 72% yield (Scheme 5 and Table 1, entry 1). This yield is comparable to that obtained in solution using 1-(1-phenylethyl)-2-methyleneaziridine.[4b] The optimized conditions differed from the solution phase reaction in several respects. Not unexpectedly, higher quantities of the reagents (RMgCl, CuI, and electrophile) were required to effect good conversions. With respect to the electrophile, better results were obtained using benzyl bromide in place of benzyl chloride. Furthermore, milder conditions (pH 4.5 buffer, CH_2Cl_2 (1:1 v/v)[12]) for the imine hydrolysis were needed to obtain the ketone product free of impurities derived from the polymer. Gratifyingly, for the solid-phase MCR, the purification protocol was greatly simplified. Upon completion of the imine hydrolysis, the organic phase was simply collected by passage through an Argonaut Isolute phase separation cartridge then passed directly through a plug of silica to ensure removal of remaining inorganic byproducts prior to evaporation to dryness. To establish the scope of the solid-phase MCR, a series of ketones **8**−**22** were made using this optimized protocol (Table 1). The ketones produced were formed in a high state of purity as judged by ^{1}H NMR spectroscopy and GC analysis (see Table 1 and Supporting Information). This assessment was verified by HPLC analysis conducted on selected examples. A range of Grignard reagents and electrophiles could be employed, and moderate to good yields (39−81%) were obtained in all cases. The scope and limitations of this reaction are broadly similar to the solution-phase reaction.[4] However, two differences are apparent. First, using supported aziridine **7**, a small amount of isomerization of the *gem*-dimethyl substituent was observed in one case (Table 1, entry 14). Specifically, ketone **21** was produced contaminated with a small amount (14%) of the isomeric ketone, 4,4-dimethyl-1-phenyloctan-3-one as a result of isomerization during the ring opening/alkylation sequence. This type of rearrangement has not previously been witnessed in solution using isopropylidineaziridines of this type. Second, we note that aldehydes, such as PhCHO, do not perform well as the electrophilic component in the supported process, but do give satisfactory results in solution.[4]

To conclude, we have developed methodology for the synthesis of Merrifield resin-bound methyleneaziridines. These supported materials can be used to produce a range of 1,3-disubstituted propanones by way of a three-component reaction which creates two new intermolecular carbon−carbon bonds. This solid-supported MCR[3] is expected to be more useful for chemical library generation using automated

Table 1. Synthesis of 1,3-Disubstituted Propanones **8**−**22** Using Solid-Supported Methyleneaziridines **6** and **7**

entry	aziridine	Grignard (R^1MgX)	electrophile (R^2X)	ketone[a]	% yield[b]	GC purity[c]
1	**6**	*n*-C_4H_9MgCl	$PhCH_2Br$	**8**	72	>94%
2	**6**	*n*-C_4H_9MgCl	(2-naphthyl)CH_2Br	**9**	56	>97% (>96%)
3	**6**	*n*-C_4H_9MgCl	4-$MeOC_6H_4CH_2Cl$	**10**	81	>96%
4	**6**	*n*-C_4H_9MgCl	Cyclohexene oxide	**11**[d]	59	>96%
5	**6**	*c*-HexMgCl	$THPOCH_2CH_2CH_2Br$	**12**	58	>99% (>99%)
6	**6**	*c*-HexMgCl	$PhCH_2Br$	**13**	70	>99%
7	**6**	*c*-HexMgCl	CH_2=$CHCH_2CH_2Br$	**14**	61	>98%
8	**6**	*c*-HexMgCl	CH_2=$CHCH_2Br$	**15**	64	>97%
9	**6**	*c*-HexMgCl	CH_3C≡CCH_2Br	**16**	53	>98%
10	**6**	EtMgCl	4-$BrC_6H_4CH_2Br$	**17**	70	>98%
11	**6**	$(CH_3)_2CHCH_2MgCl$	$PhCH_2Br$	**18**	64	>91%
12	**6**	$(CH_3)_2CHCH_2MgCl$	(2-naphthyl)CH_2Br	**19**	64	>95% (>94%)
13	**6**	$PhCH_2MgCl$	$PhCH_2Br$	**20**	40	>92% (>94%)
14	**7**	*n*-C_4H_9MgCl	$PhCH_2Br$	**21**[e]	74	>99%
15	**7**	$(CH_3)_2CHCH_2MgCl$	CH_2=$CHCH_2CH_2Br$	**22**	39	>99%

[a] All of the ketones have been fully characterized (see Supporting Information). [b] Yields are based on resin loadings for **6** and **7** determined by combustion analysis. [c] Additional values reported in parentheses obtained by HPLC analysis. [d] Additional washings with methanol prior to imine hydrolysis. [e] This material was contaminated with 4,4-dimethyl-1-phenyloctan-3-one (ca. 14%).

techniques than its solution-phase counterpart. Efforts to develop other MCRs of supported methyleneaziridines are continuing in our laboratories.

(11) The NMR measurements were conducted as described by Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. The benzyl ether of **1** was prepared (NaH, BnCl, cat. Bu_4NI, DMF, 74%) and used for comparison purposes in the ^{13}C gel-phase NMR analysis (see Supporting Information).

(12) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 221.

Acknowledgment. We are indebted to Syngenta and the University of Warwick for financial support.

Supporting Information Available: ^1H NMR spectra and experimental procedures for the preparation of **1**−**4** and **6**−**22**; ^{13}C gel-phase NMR spectra and preparative methods for **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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