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ROMPgel-Supported Thiazolium Iodide: An Efficient Supported Organic Catalyst for Parallel Stetter Reactions

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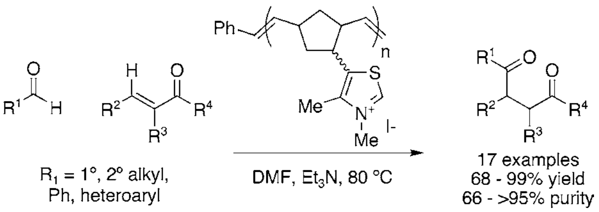
ABSTRACT



A high-loading ROMPgel-supported thiazolium iodide was prepared via ROMPolymerization of the corresponding norbornene-derived monomer. The resulting ionic ROMPgel proved to be an efficient organic catalyst for Stetter reactions. The 1,4-dicarbonyl products, important intermediates in the synthesis of cyclopentenones and heterocycles, were obtained in high yields and excellent purities after minimal purification. The ROMPgel could be reused in up to four consecutive reaction cycles without significant loss of catalytic activity.

The continued development of clean, rapid, and efficient methods to generate compound libraries containing a wide range of chemical diversity remains a strategically important challenge in the pharmaceutical and agrochemical industry. To address this need, considerable research interest has recently focused on the development of new and improved polymer-supported reagents, catalysts, and scavengers for use in solution-phase parallel synthesis.[1] Polymer-assisted solution-phase synthesis provides advantages over traditional solution-phase organic synthesis and classical solid-phase organic synthesis (SPOS), allowing rapid reaction optimization and scale-up in both sequential and multistep syntheses. Purification is simplified since only filtration and washing procedures are required, while reaction progress is easily monitored through classical solution-phase methods.

ROMPgel is a general class of high-loading polymer-supported reagents, catalysts, or scavengers, derived from ring-opening metathesis polymerization (ROMPolymerization) of substituted norbornene and 7-oxanorbornene monomers.[2] The monomers are readily prepared in solution through a small number of steps and then purified and fully characterized prior to ROMPolymerization. In the presence of a cross-linker, numerous well-defined polymers with respect to molecular weight and polydispersity have been prepared and used in “purification free” parallel synthesis.[2]

Continuing our interest in the rapid introduction of chemical diversity and preparation of functionalized building blocks through simplified parallel synthesis, we investigated the synthetically underutilized Stetter reaction.[3] The Stetter reaction and related benzoin and acyloin condensations represent important classes of umpolung reactivity. Reversal of the reactivity at a carbonyl carbon atom of an aldehyde,

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(1) (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *23*, 3815−4195. (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650−679.

(2) (a) Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Chem. Rev.* **2002**, *102*, 3301−3324. (b) Flynn, D. L.; Hanson, P. R.; Berk, S. C.; Makara, G. M. *Curr. Opin. Drug Discuss. Dev.* **2002**, *5*, 571−579. (c) Barrett, A. G. M.; Hopkins, B. T.; Love, A. C.; Tedeschi, L. *Org. Lett.* **2004**, *6*, 835−837.

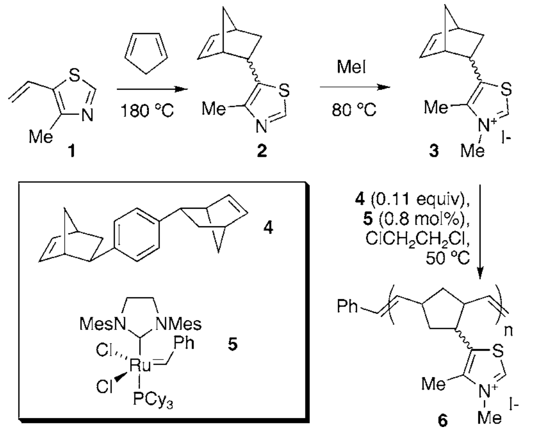
(3) (a) Stetter, H.; Schreckenberg, M.*Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81−81. (b) Stetter, H.; Kuhlmann, H. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 539−539. (c) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639−647. (d) Stetter, H.; Kuhlmann, H. *Org. React.* **1991**, *40*, 407−496. (e) Stetter, H.; Haese, W. *Chem. Ber.* **1984**, *117*, 682−693.

10.1021/ol048694u CCC: $27.50

to provide a nucleophilic (d^1) entity (umpolung),[4] and subsequent transformations showing the nucleophilic addition of acyl-anions to acceptors bearing an activated double bond have recently attracted considerable research interest.[5] Reactions may be traditionally catalyzed by cyanide ions or thiazolium salts (and more recently 1*H*-imidazolium and triazolium salts),[5] under basic conditions. While the mechanism for cyanide catalysis is well established,[6] contention as to the nature of the active catalytic azolium species remains.[5b] The Stetter reaction is an efficient method for the generation of 1,4-dicarbonyl compounds, important intermediates in the synthesis of cyclopentenone derivatives[7] and heterocycles, including furans,[8] pyrroles,[9] pyrrolidines,[10] and thiophenes.[11] The thiazolium-catalyzed Stetter reaction has recently been successfully employed in SPOS,[12] but attempts to attach the catalyst to a polymer have not always provided satisfactory results.[13] Usually lower yields were obtained than when using soluble thiazolium salts, and often the catalysts could only be partially regenerated, so they rapidly lost their effectiveness. 1,4-Diketones were recently synthesized using a solid-supported reagent, i.e., thiazolium salt−DBU−Al_2O_3,[14] under microwave irradiation.[15] This system allowed for reduced reaction times and the preparation of synthetically challenging γ-diketones from aromatic aldehydes in good yields. The development of a task-specific ionic liquid (TSIL), effectively replacing the polymeric support with an imidazolium salt, was recently shown to promote a Stetter reaction with minimal purification.[16] However, this approach introduces additional steps in attaching and detaching the ionic liquid component and reduces possible structure diversity. Applying ROMPgel methods, we investigated the preparation of a supported thiazolium iodide catalyst **6** for application in parallel Stetter reactions (Scheme 1).

The Diels−Alder reaction between commercially available 4-methyl-5-vinyl-1,3-thiazole (**1**) and cyclopentadiene gave a (1:9.5) mixture of *exo* and *endo* cycloadducts (**2**) (53% yield). Quarternization of **2** with iodomethane gave the thiazolium salt monomer, which was polymerized in the presence of cross-linker **4**[2c] (11 mol %), using the second-generation Grubbs catalyst **5** to give the ROMPgel **6** with a loading of 2.52 mmol g^{-1}.

Scheme 1. Preparation of ROMPgel-Supported Thiazolium Iodide



After considerable experimentation, we found the ROMPgel **6** catalyzed the Stetter reaction in DMF in the presence of either DBU, 1,1,3,3-tetramethylguanidine, or triethylamine, in similar yield and purity. However, in terms of practicality, successful recovery of the active catalyst on completion of the reaction was only achieved when triethylamine was used as the base. The catalyst was recovered by filtration, rinsed, and reused in a further four consecutive reactions without significant loss in catalytic activity. Despite the associated high reactivity of the aldehyde, often resulting in high yields of self-condensation or benzoin products,[13] we were pleased to observe preferential reaction of equimolar quantities of aliphatic aldehydes with α,β-unsaturated ketones via the Stetter reaction pathway. Addition of alcohol cosolvents (*n*-BuOH, *i*-PrOH) promoted small increases in relative reaction rates, but only partial recovery of active catalyst was possible. In an attempt to increase the rate of reaction, the effect of polymer architecture on the swelling properties was also investigated. Previous work using ROMPgel-supported ethyl 1-diazo-2-oxopropyl-phosphonate revealed that significant increases in the relative reaction rates could be achieved through addition of a more polar comonomer.[2c] Unfortunately, the addition of more polar comonomers failed to provide any significant rate increase. ROMPgel **6** catalyzed the equimolar addition of aliphatic aldehydes to a number of electron-deficient double bonds in near quantitative yield (Table 1). The reaction proceeded in very high purity with electron-withdrawing aryl substituents on either, or both, sides of the α,β-unsaturated system. Reactions proceeded well in the presence of ortho and para substituents. High purities were also obtained with electron-donating aryl substituents on either, or both, sides of the α,β-unsaturated system, but slightly longer reaction times were required to ensure complete conversion. The Stetter reaction between an aryl aldehyde and enone (**8m**) was found to proceed with

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(4) Seebach, D. *Angew. Chem.* **1979**, *91*, 259−278. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258.

(5) (a) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326−1328. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541.

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(8) El-Haji, T.; Martin, J. C.; Descotes, G. J. *J. Heterocycl. Chem.* **1983**, *20*, 233−235.

(9) Perrine, D. M.; Kagan, J.; Huang, D.-B.; Zeng, K.; Theo, B.-K. *J. Org. Chem.* **1987**, *52*, 2213−2216.

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(11) Wynberg, H.; Metselaar, J. *Synth. Commun.* **1984**, *14*, 1−9.

(12) (a) Kobayashi, N.; Kaku, Y.; Higurashi, K.; Yamauchi, T.; Ishibashi, A.; Okamoto, Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1747−1750. (b) Raghavan, S.; Anuradha, K. *Tetrahedron Lett.* **2002**, *43*, 5181−5183. (c) Kobayashi, N.; Okamoto, Y.; Higurashi, K.; Kaku, Y.; Ishibashi, A.; Yamauchi, T. PCT Int. Appl. WO 03/062230 A1 2003.

(13) (a) Castells, J.; Dunach, E.; Geijo, F.; Pujol, F.; Segura, P. M. *Isr. J. Chem.* **1978**, *17*, 278−283. (b) Sell, C. S.; Dorman, L. A. *J. Chem. Soc., Chem. Commun.* **1982**, 629−630. (c) Chang, B.-H.; Chang, Y. L. *J. Chin. Chem. Soc.* **1983**, *30*, 55−58. (d) Ho, T.-L.; Liu, S.-H. *Synth. Commun.* **1983**, *13*, 1125−1127.

(14) DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

(15) Yadav, J. S.; Anuradha, K.; Subba Reddy, B. V.; Eeshwaraiah, B. *Tetrahedron Lett.* **2003**, *44*, 8959−8962.

(16) Anjaiah, S.; Chandrasekhar, S.; Grée, R. *Tetrahedron Lett.* **2004**, *45*, 569−571.

Table 1. Yields and Purities of γ-Diones

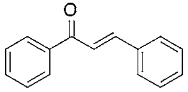
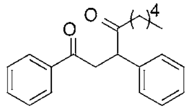
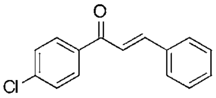
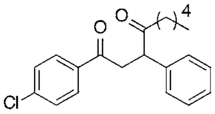
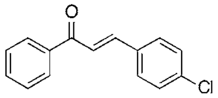
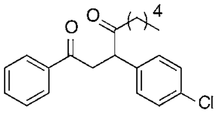
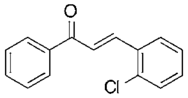
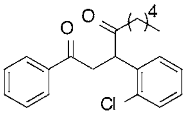
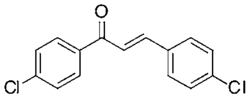
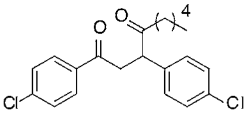
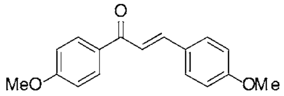
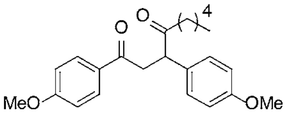
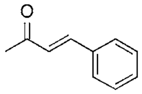
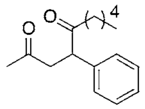
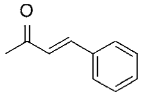
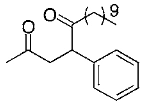
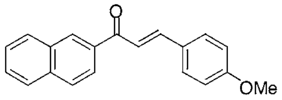
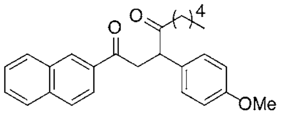
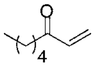
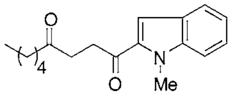
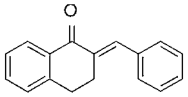
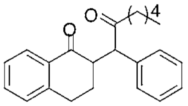
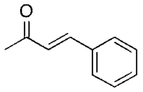
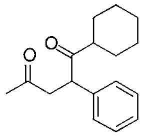
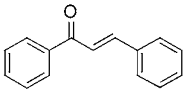
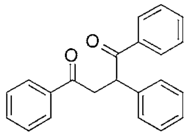
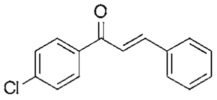
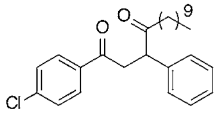
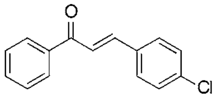
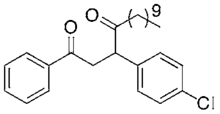
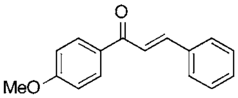
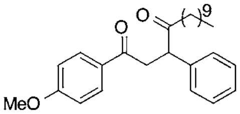
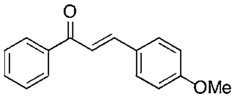
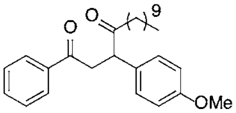
	α,β-unsaturated ketone	Time (h)		1,4-dicarbonyl	% yield (% purity)[a]
8a		22	**9a**		89 (90)[b]
8b		22	**9b**		92 (95)
8c		24	**9c**		98 (>95)
8d		22	**9d**		97 (>95)
8e		26	**9e**		92 (95)
8f		32	**9f**		86 (>95)
8g		20	**9g**		95 (>95)
8h		28	**9h**		95 (90)
8i		38	**9i**		98 (85)[c]
8j		32	**9j**		86 (94)
8k		68	**9k**		69 (66)[d]
8l		38	**9l**		82 (82)
8m		72	**9m**		68 (73)[c]
8n		28	**9n**		97 (>95)
8o		28	**9o**		99 (>95)

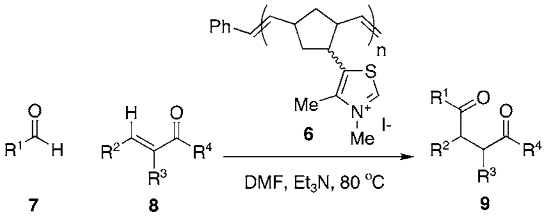
Table 1. (Continued)

8p		38	**9p**		94 (>95)
8q		39	**9q**		87 (>95)

[a] Yields refer to isolated products. Purities as judged by ^{1}H and ^{13}C NMR spectra, GC-MS, and microanalysis. [b] **7a** (1.4 equiv) was used used; 7-hydroxydodecan-6-one (5%) was observed as a side product. Daynard, T. S.; Eby, P. S.; Hutchinson, J. H. *Can. J. Chem.* **1993**, *71*, 1022−1028. Fleming, I.; Roberts, R. S.; Smith, S. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1215−1228. [c] **7i** (1.4 equiv) was used; 7-hydroxydodecan-6-one (5%) was observed as a side product. [d] **8k** (30%). [e] 2-Hydroxy-1,2-diphenylethanone (**10k**) (14%) was observed as a side product.

moderate selectivity; competing benzoin[17] product formation (14% yield) was also observed. Reaction of a heteroaromatic aldehyde with an aliphatic enone was found to give the desired Stetter product **9j** in 86% yield, along with 6% recovered aldehyde.

Scheme 2. Parallel Synthesis of 1,4-Dicarbonyls Using a ROMPgel-Supported Thiazolium Iodide



In conclusion, a high-loading ROMPgel-supported thiazolium iodide **6** has been prepared in three steps from commercially available compounds. The immobilized catalyst was found to catalyze the equimolar addition of aliphatic aldehydes to a range of enones to provide the corresponding γ-diones in both high yields and purities. The 1,4-dicarbonyl products are important intermediates in the synthesis of cyclopentenones[7] and heterocycles, including furans,[8] pyrroles,[9] pyrrolidines,[10] and thiophenes,[11] allowing rapid introduction of skeletal and chemical diversity. The ROMPgel catalyst could be readily recovered and reused in a further four consecutive reactions with no significant loss in activity.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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