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Polymer-supported electron-rich diene for hetero Diels–Alder reactions

Camille Pierres,[a] Pascal George,[b] Luc van Hijfte,[c,†] Jean-Bernard Ducep,[c] Marcel Hibert[a] and André Mann[a,*]

[a]*Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081, Faculté de Pharmacie, 74, route du Rhin, F-67401 Illkirch, France*
[b]*Département de Recherche SNC Laboratoire de Recherche Sanofi-Synthelabo, 31 av. P. V. Couturier, F-92220 Bagneux, France*
[c]*Sanofi-Synthelabo Recherche, Département de Recherche Exploratoire, 16, rue d'Ankara, F-67000 Strasbourg, France*

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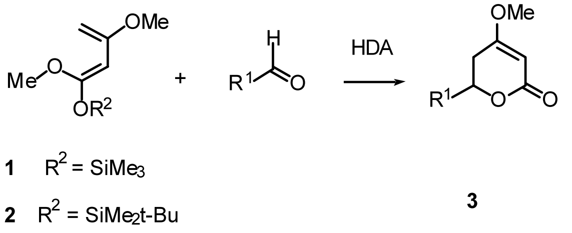
Abstract—A Brassard diene analogue was grafted on a modified Merrifield resin and used in a hetero Diels–Alder reaction with various aldehydes or ketones. The reaction gave access to 6-substituted 5,6-dihydropyrones (**5a**–**u**). This new immobilized electron-rich diene is more stable than the corresponding native diene, and is a versatile supported reagent. © 2003 Elsevier Science Ltd. All rights reserved.

One of the most powerful reactions in the repertoire of synthetic organic chemists is the Diels–Alder reaction, highly suitable for the construction of carbo- and heterocycles.[1] In recent years solid-supported Diels–Alder reactions have been used for the construction of libraries.[2] In the present communication, we report on the use of a hetero Diels–Alder (HDA) reaction performed on a solid support towards the preparation of a set of 5,6-dihydropyrones **3**. It must be emphasized that the pyridone platform is present in several bioactive compounds from natural[3] or synthetic sources.[4] One of most direct accesses to the pyrone of type **3** is based on a HDA reaction between the electron-rich Brassard diene (**1**)[5] and a suitable aldehyde or ketone in the presence of a Lewis acid (Scheme 1).



Scheme 1.

For the preparation of a library of pyrones, we planned to use the HDA reaction by grafting the diene **1** on a solid support and let it react with aldehydes or ketones. From literature reports we noticed that diene **1** seemed to be a very sensitive reagent to handle. Some preliminary experiments in solution with diene **1** confirmed our expectation. In our hands, the conditions reported by Midland[6] or Castellino[7] for the HDA reaction of aldehydes with the Brassard diene **1** did not give reproducible yields, furthermore with ketones the HDA reaction seemed sluggish and low yielding.

The Brassard diene **1** was mostly destroyed in the presence of the Lewis acid catalyst before it reacted with aldehydes. Therefore in diene **1**, we decided to replace the trimethylsilyl appendage on the silyl enol ether with the corresponding *tert*-butyldimethyl group, a more robust protection for the oxygen atom.[8–10] Indeed, when diene **2** was added slowly at −78°C to a mixture of the aldehyde and the Lewis acid (Me_2AlCl or Et_2AlCl) in a CH_2Cl_2 solution, the HDA adducts were obtained in reproducible yields (55–65%). As CH_2Cl_2 is recommended for its swelling properties in supported chemistry, we confidently embarked in the preparation of **E** (a resin immobilizing diene **2**) in order

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Keywords: solid supported reagent; hetero Diels–Alder; 5,6-dihydropyrones.

* Corresponding author. Tel.: +33-090-242-227; fax: +33-090-244-310; e-mail: andre.mann@pharma.u-strasbg.fr

† Present address: Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen-Cilag, Campus de Maigremont, BP 615, F-27106 Val de Reuil Cedex, France.

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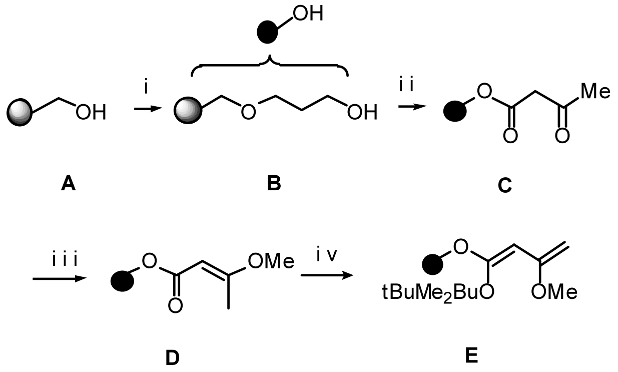
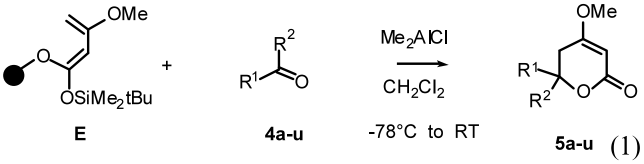


Scheme 2. *Reagents and conditions*: (i) for the preparation of **B** see Ref. 10; (ii) diketene, DMAP, CH_2Cl_2, −50°C to rt; (iii) $HC(OMe)_3$, H_2SO_4 (cat.) then heating at 60°C; (iv) a. LDA, THF, −78°C then rt, b. DMPU, *t*$BuMe_2SiCl$, −78°C then rt.

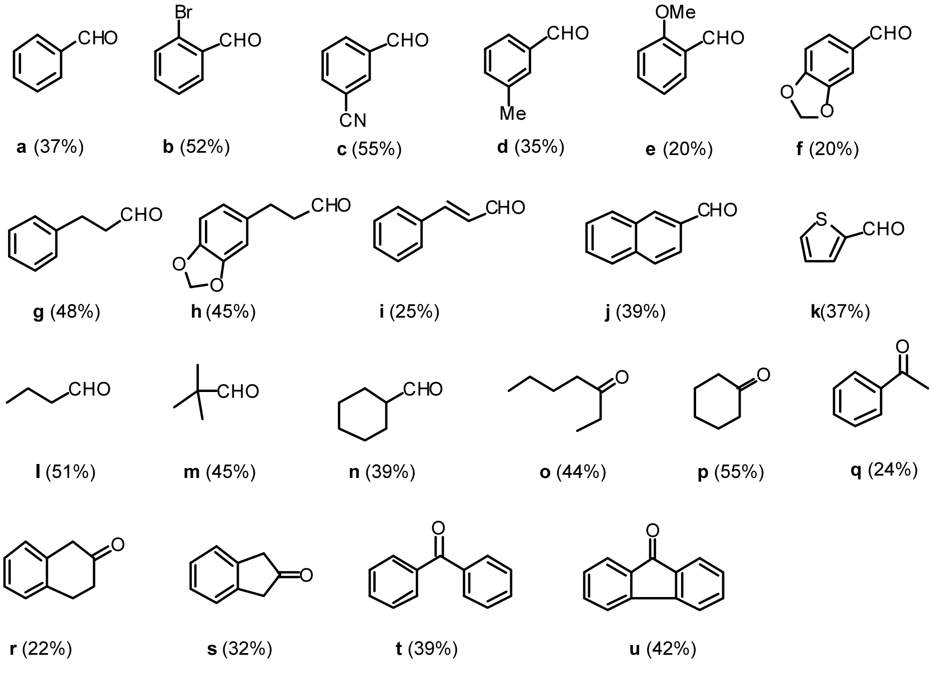
to explore its capacity to produce pyrones in an HDA reaction. The preparation of this resin is summarized in Scheme 2. As strong basic conditions are required for the obtention of **E**, we used a propanol spacer, following a procedure recommended by Tietze in a similar case.[11] First the propanol spacer was attached to a Merrifield (**A**) resin[12] and then the resulting resin **B** was functionalized with the β-keto-ester residue by the diketene route, yielding **C**. The resin **D** was obtained by a short treatment of **C** with an excess of orthoformate in the presence of traces of sulfuric acid at room temperature, and then the resin was heated at 60°C in vacuo to complete the enol ether formation. Then resin **D** was taken up in THF and treated at −78°C with LDA in the presence of DMPU for 2 h, and quenched with an excess of *t*$BuSiMe_2Cl$ to lead to resin **E**. All the chemical transformations of the solid support have been monitored by ^{13}C NMR using the procedure of Wagner and Mioskowski.[13] In some cases, when a transformation was judged incomplete, a second cycle was performed. Resin **E** can be considered as a solid supported reagent, with some advantages over the native diene **2**. Indeed resin **E** can be stored for several months at −18°C without notable alteration, whereas **2**, even in solution, is rapidly altered.

The reactivity of resin **E** in the HDA reaction with various aldehydes and ketones was then examined. We experimented several Lewis acids, among them $BF_3{\cdot}Et_2O$, $ZnCl_2$ or $MgBr_2$, but Me_2AlCl was by far the best activator. Our results are depicted in Table 1. The best experimental procedure was the following: the aldehyde or ketone (2.5 equiv.) was dissolved in CH_2Cl_2 at −50°C, Me_2AlCl (2.5 equiv.) was added, followed by the resin **E** (1 equiv.), and the reaction mixture was gently stirred overnight from −50°C to rt. Then the resin was washed with CH_2Cl_2 and MeOH, the solvent concentrated, and the residue rapidly filtered through a short path of silica gel, eluting with a mixture of AcOEt/heptane (1/1) to get the desired product with a purity higher than 95%. As it appears in Table 1, the dihydropyrones **5a–u** were obtained with various types of aldehydes or ketones **4a–u**. The yields seem moderate but are at least comparable to the reaction performed in solution, because they are based on the loading level of the benzylic alcohol in the Merrifield support (six steps overall). Interestingly pyrones **5h–i** are kawalactones.[15]



(1)

Table 1. Aldehydes and ketones (**4a–u**) used in the HDA reaction (Eq. (1)) with resin **E**. The yields for the isolated adducts **5a–u** are in brackets[14]



In conclusion the present work demonstrated that 6-substituted 5,6-dihydropyrones can be prepared by an HDA reaction with the immobilized diene **2** on a modified Merrifield resin and a wide range of aldehydes or ketones. Furthermore diene **2** grafted on resin **E** is a *stable supported reagent* which may offer significant short-cuts for the preparation of libraries of 5,6-dihydropyrones and for the production of chemical complexity in few chemical steps.[16]

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    Physical data for resins: (**B**) ^{13}C NMR (75 MHz, C_6D_6/CCl_4) δ 72.6, 68.0, 59.8, 40.1, 32.3. (**C**) ^{13}C NMR (75 MHz, C_6D_6/CCl_4) δ 198.3, 166.1, 72.5, 65.9, 62.0, 49.4, 40.3, 40.2, 28.9. (**D**) ^{13}C NMR (75 MHz, C_6D_6/CCl_4) δ 172.2, 166.4, 90.8, 72.5, 66.5, 60.2, 54.6, 40.3, 29.4, 18.5. (**E**) ^{13}C NMR (75 MHz, C_6D_6/CCl_4) δ 158.4, 79.2, 76.9, 72.2, 66.1, 64.6, 53.4, 40.2, 29.3, 25.7, 17.9, −3.9.
14. Selected physical data for some 5,6-dihydropyrones: **5c** R_f 0.28 (AcOEt/heptane: 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.44 (m, 4H), 5.45 (X part from a ABXM system, dd, *J* 12 and 4 Hz, 1H), 5.25 (M part from a ABXM system, d, *J* 1.5 Hz, 1H), 3.80 (s, 3H), 2.70 (AB part from a ABXM system, *J* 17, 12, 4 and 1.5 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 172.2, 166.1, 132.2 to 129.1, 118.8, 90.5, 75.5, 56.3, 34.7. **5h**: R_f 0.25 (AcOEt/hept: 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74–6.64 (m, 3H), 5.92 (s, 2H), 5.14 (X part from a ABXM system, d, *J* 1.6 Hz, 1H), 4.35 (M part from a ABXM system, m, 1H), 3.73 (s, 3H), 2.85–2.65 (m, 2H), 2.39 (AB part from a ABXM system, *J* 17.2, 12.2, 4.1 and 1.6 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 172.7, 167.3, 147.2, 145.9, 134.6, 121.3, 108.9, 108.3, 100.8, 90.4, 74.6, 55.9, 36.6, 33.0, 30.6. **5m**: R_f 0.35 (AcOEt/hept: 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (d, *J* 1.9 Hz, 1H), 4.03 (dd, *J* 13.1 and 3.6 Hz, 1H), 3.74 (s, 3H), 2.38 (AB part from ABXM system, *J* 17, 13.1, 3.6 and 1.9 Hz, 2H), 1.01 (m, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 173.4, 167.7, 90.1, 83.2, 56.0, 33.6, 28.4, 25.4. **5r** R_f 0.32 (AcOEt/hept: 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16–7.02 (m, 4H), 5.22 (s, 1H), 3.77 (s, 3H), 3.09 (AB system, *J* 16.2 Hz, 2H), 3.15–3.01 (m, 1H), 2.86–2.76 (m, 1H), 2.50 (AB system, *J* 17.2 Hz, 2H), 2.33–2.03 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 171.1, 166.3, 134.3, 132.7, 129.3, 128.6, 126.3, 126.1, 90.1, 78.3, 55.9, 40.1, 36.3, 32.8, 25.9.
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