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"Traceless" Solid-Phase Synthesis of Furans via 1,3-Dipolar Cycloaddition Reactions of Isomünchnones

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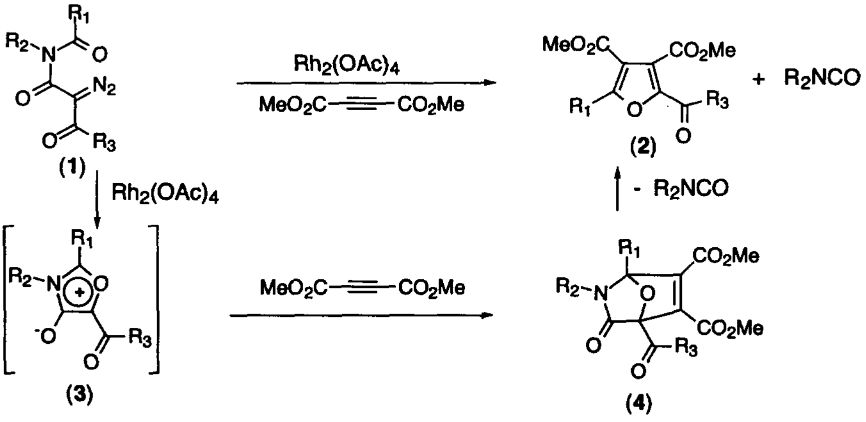
Abstract: The generation and cycloaddition reactions of polymer-supported mesoionic isomünchnones derived from α-diazocarbonyl intermediates is described in this report. This chemistry provides a method for preparing combinatorial libraries of functionalized furans and features cycloreversion as a new synthetic strategy for "traceless" synthesis of small organic molecules. © 1997 Elsevier Science Ltd.

Combinatorial chemistry has rapidly become a key tool in contemporary pharmaceutical research.[2] To date, the most widely used synthetic techniques in combinatorial chemistry rely on solid-phase organic synthesis,[3] though solution-phase strategies are gaining increased appeal as evidenced by recent creative applications of polymer-supported reagents and scavengers,[4] as well as multi-phase liquid systems employing fluorous solvent/reagent combinations.[5] While numerous different organic reactions have now been shown to be amenable to a solid-phase approach, relatively few examples have utilized transformations of highly reactive species such as radicals, carbenes, nitrenes, acyliminium species, etc.[3a] In this report we describe the reactions of polymer-supported rhodium carbenoids derived from α-diazocarbonyl compounds in a synthesis of furans that features cycloreversion chemistry as a new "traceless" linkage strategy.

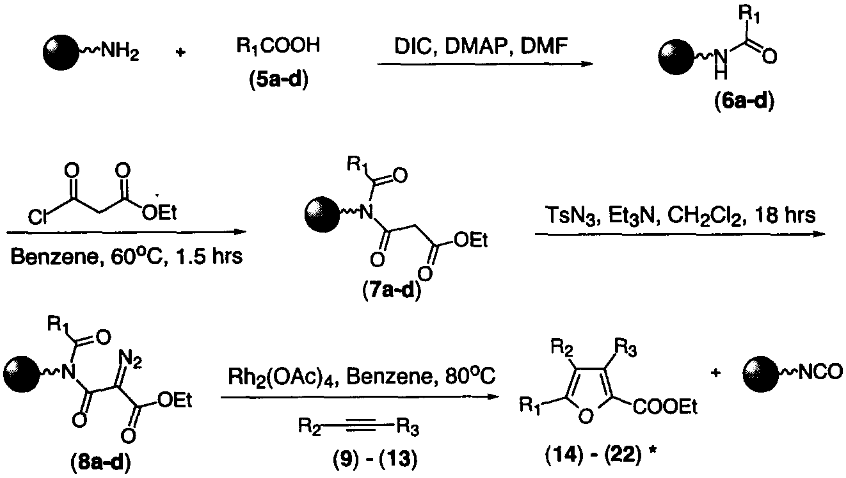
Scheme I



α-Diazocarbonyls of the type (1) react with Rh(II) catalysts in the presence of electron-deficient acetylenes (e.g. dimethyl acetylenedicarboxylate, DMAD) to give furan derivatives (2) (Scheme I). The first step in this transformation is formation of a highly reactive rhodium (II) carbenoid that collapses to a mesoionic dipole intermediate, 1,3-oxazolium-4-oxide (3), also known as an isomünchnone. Isomünchnones readily undergo [2 + 3] cycloaddition reactions with acetylenes to give bicyclic intermediates (4), followed by cycloreversion with loss of isocyanate affording furans (2).[6] The starting materials required for construction of the precursor α-diazoimide (1) are readily available primary amines, carboxylic acids and malonic or acetoacetic acid derivatives. Analysis of the mechanism (Scheme I) indicates, however, that the starting amine is not incorporated into the final furan product and hence cannot contribute to the diversity of combinatorial furan libraries. We decided, therefore, to use this position as a point of attachment to the solid support, and to dispense with a conventional cleavable linker for furan synthesis. Following cycloaddition of the acetylene, extrusion of a resin-bound isocyanate liberates the furan into solution and leaves no obvious remnant of polymer tethering in the desired product.[7,8]

Solid-phase furan synthesis was carried out as shown in Scheme II. TentaGel™-NH_2 resin was acylated with carboxylic acids using diisopropylcarbodiimide (DIC) in the presence of catalytic amounts of DMAP.[9] Conversion of amide (**6**) to the imide (**7**) was accomplished by treating the resin twice with a 1:1 (v/v) mixture of the malonyl chloride in benzene at 60°C for 1.5 hours. Quantitative diazo-transfer to imide (**7**) was effected at room temperature using tosyl azide in CH_2Cl_2/NEt_3. Optimization of this reaction sequence was facilitated by using gel-phase ^{13}C-NMR to monitor transformation of resin initially acetylated with 2-^{13}C-labeled Ac_2O.[10] This analysis indicated that both the imide and diazoimide formation steps proceeded with >95% conversion. Diazoimides (**8**) were reacted with different acetylenes (**9**) - (**13**) in benzene at 80 °C for 2 hours in the presence of $Rh_2(OAc)_4$ as catalyst. Solvent was then removed by filtration, the resin washed with CH_2Cl_2, and the combined organic fractions were washed with water to remove any traces of rhodium catalyst. Analysis of the crude products by TLC showed exclusively the presence of the desired furans (**14**) - (**22**) and excess unreacted acetylene. The products were further purified by column chromatography and fully characterized.[11] In the preparation of a series of substituted furans derived from ethyl malonyl chloride, isolated yields for the pure materials (calculated on the basis of initial resin loading) ranged from 50-70% (see Table).

Scheme II



a: $R_1 = CH_3$; **b**: $R_1 = CH_2CH_2Ph$; **c**: R_1 = 4-MeO-C_6H_4; **d**; $R_1 = {}^{13}CH_3$

Acetylenes: (**9**) dimethyl acetylenedicarboxylate (DMAD); (**10**) dibenzoylacetylene; (**11**) diethyl acetylenedicarboxylate (DEAD); (**12**) methyl propiolate; (**13**) ethyl propiolate

* For description of R_1, R_2 and R_3 in (**14**)- (**22**) see Table

To avoid contamination of the desired furan product with residual acetylene a two step sequence was implimented for the cycloaddition reaction. In this experiment the ^{13}C-labeled diazoimide (**8d**) was reacted with 10 equivalents of DMAD in the presence of $Rh_2(OAc)_4$ at *room temperature* in anticipation of trapping the bicyclic intermediate (**4**) on the polymer support. Excess acetylene was washed away and the resin taken into fresh solvent and heated at 80°C to promote the cycloreversion. HPLC analysis of the crude product from this reaction showed a single peak corresponding to the furan (**22**) with neither starting acetylene nor other impurities being observed. Resin washings did not contain any ^{13}C label indicating that no cycloreversion occurred at room temperature, while gel-phase ^{13}C NMR of the resin after thermolysis showed no resonances from enriched carbons and suggested that cycloaddition to the isomünchnone proceeded efficiently at room temperature.

This stepwise room temperature / thermal cycloreversion sequence failed to provide furans from propiolate esters (**12**) and (**13**). These acetylenes, activated by a single electron withdrawing moiety, are less reactive than DMAD and do not undergo additions to the immobilized dipoles at an appreciable rate at ambient temperature.[12] However, these lower propiolates are sufficiently volatile that one can employ an excess of acetylene in cycloadditions carried out at 80°C, followed by removal of the unreacted dipolarophile *in vacuo* to provide furans of high purity.

Table

Entry	Diazoimide	Acetylene	Furan	%Yield
1	**8a**	**9**	**14**; R_1=CH_3, R_2=R_3=CO_2CH_3	70
2	**8a**	**10**	**15**; R_1=CH_3, R_2=R_3=COPh	50
3	**8b**	**9**	**16**; R_1=CH_2CH_2Ph, R_2=R_3=CO_2CH_3	58
4	**8b**	**11**	**17**; R_1=CH_2CH_2Ph, R_2=R_3=$CO_2CH_2CH_3$	62
5	**8c**	**9**	**18**; R_1=4-OMeC_6H_4, R_2=R_3=CO_2CH_3	63
6	**8c**	**11**	**19**; R_1=4-OMeC_6H_4, R_2=R_3=$CO_2CH_2CH_3$	60
7	**8a**	**12**	**20**;[#] R_1=CH_3, R_2= CO_2CH_3, R_3=H	56
8	**8b**	**13**	**21**;[#] R_1=CH_2CH_2Ph, R_2= $CO_2CH_2CH_3$, R_3=H	51
9	**8d**	**9**	**22**; R_1=$^{13}CH_3$, R_2=R_3=CO_2CH_3	67

\# Compounds (**20**) and (**21**) are formed as single regioisomers, with the regiochemistry being assigned based on NOE experiments. This regiochemical preference is in accordance with the earlier observations of Padwa.[6d]

To further demonstrate the utility of this solid phase chemistry, we generated a small (32 member) combinatorial library of furans via split synthesis using eight carboxylic acids, two malonyl chlorides, and two acetylenes as shown in Scheme III. The library was synthesized as four pools comprising eight compounds each using the stepwise cycloaddition sequence described above.[13] HPLC analysis of each pool showed the expected eight peaks with negligible impurities. HPLC of one representative pool is given in the Figure below.

Scheme III

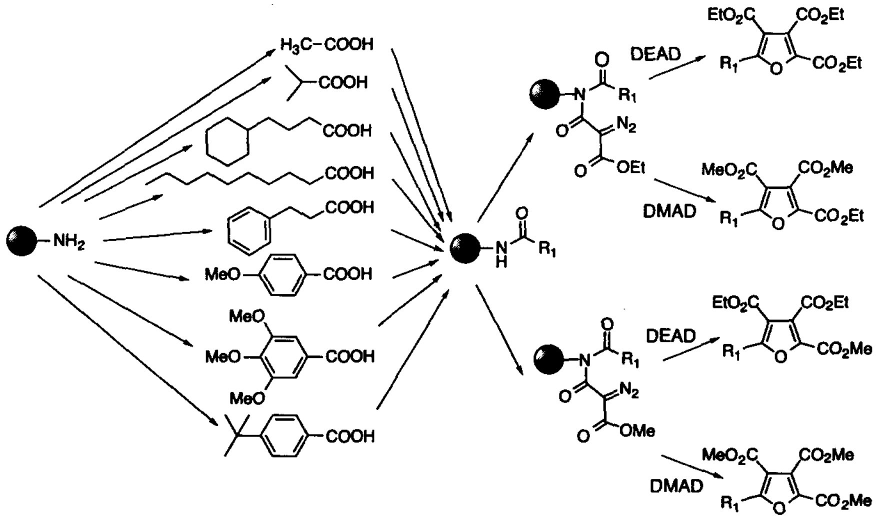
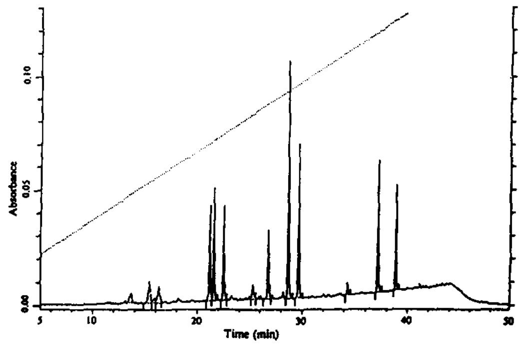


Figure: *HPLC absorbance (260 nm) of one pool from the furan library.*



In summary, we have developed an efficient solid-supported synthesis of diazoimides and have demonstrated their rhodium-catalyzed transformation into reactive 1,3-dipolar intermediates, which participate in cycloaddition reactions with acetylenes to afford variously substituted furans. This strategy exploits a thermally promoted isocyanate extrusion reaction for liberating the fully elaborated product from the resin and offers a new approach towards combinatorial libraries of functionalized furans.

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9. TentaGel™-NH_2 resin (purchased from Rapp Polymere, Tubingen, Germany) does not contain secondary amide bonds in the polymer/linker backbone and hence is a suitable support for selective imide synthesis.
10. The ^{13}C resonances for the labeled methyl group in amide (**6d**), imide (**7d**) and diazoimide (**8d**) appear at 23.3, 25.9 and 24.2 ppm respectively. For a detailed description of the gel-phase NMR method, see Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588.
11. All products gave satisfactory proton NMR, and HRMS spectra.
12. Note that the requirement for using electron-deficient alkynes in this cycloaddition chemistry does significantly restrict access to a wider range of structurally diverse furan libraries.
13. 100 mg aliquots of TentaGel-NH_2 resin were separately subjected to DMAP-catalyzed reactions with eight carboxylic acids (10 eq.) using DIC (5 eq.) as a coupling agent in DMF for 16 hours. The resins were washed with DMF, CH_2Cl_2, MeOH, Et_2O, then the products amides mixed and split into two portions and separately treated twice with methyl malonyl chloride and ethyl malonyl chloride (2 ml of 1:1 v/v solution in benzene) at 65 °C for 1.5 hours. After washing, the resins were individually subjected to diazo-transfer reactions with tosyl azide (7.5 eq., 0.75 M in CH_2Cl_2) using NEt_3 (15eq.) as base for 24 hours. Resins were washed with CH_2Cl_2 and the resulting two pools of diazoimides were further split in to two portions and reacted separately at room temperature for 4 hours with 1 M solutions of DMAD and DEAD in benzene (10 eq.) using 0.1 eq. $Rh_2(OAc)_4$ as catalyst. Excess acetylene was removed by washing with benzene and the resin then heated in fresh anhydrous benzene (2 ml) at 80 °C for 1.5 hours to promote the cycloreversion. Solvent was removed by filtration and the resin washed with CH_2Cl_2. The combined organic filtrates were washed with water to remove any traces of catalyst present and solvent was removed in vacuo after drying over Na_2SO_4.

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