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Solid-Phase Synthesis of Amino Acid Derived *N*-Unsubstituted Pyrazoles via Sydnones

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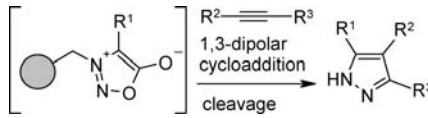
ABSTRACT



A new method to synthesize *N*-unsubstituted pyrazoles on a solid support is described. The solid support acts as a protecting group for the amino acid. *N*-Protected amino acid is *N*-nitrosated, and the subsequent treatment with acetic anhydride in a microwave reactor yields mesoionic sydnones that react in situ in 1,3-dipolar cycloaddition reactions with alkynes. Traceless cleavage of the products gives *N*-unsubstituted pyrazoles in high overall yields.

Pyrazoles show a wide variety of pharmacological effects, including anti-inflammatory (celecoxib),[1] antiobesity (rimonabant),[2] alcohol dehydrogenase inhibitory (fomepizole),[3] and phosphodiesterase inhibitory (sildenafil)[4] activities. Huisgen's 1,3-dipolar cycloaddition is a versatile method to synthesize five-membered nitrogen heterocycles.[5] Recent synthesis of pyrazoles via 1,3-dipolar cycloaddition includes reactions of nitrile imines and alkynes[6] or enamines,[7] hydrazones and nitroolefins,[8] diazo compounds and alkynes,[9] and azomethine imines and alkynes.[10] Sydnones are relatively stable mesoionic compounds that react as azomethine imine-type dipoles.[11] 1,3-Dipolar cycloaddition of sydnones with alkynes has been studied by Huisgen et al.[12] Recently sydnones have been utilized in the cycloadditions yielding functionalized pyrazoles.[13] The sydnone route produces normally *N*-substituted pyrazoles because an *N*-substituted amino acid is essential to the *N*-nitrosation reaction.

Solid-phase synthesis of heterocycles and 1,3-dipolar cycloadditions on solid supports have recently been

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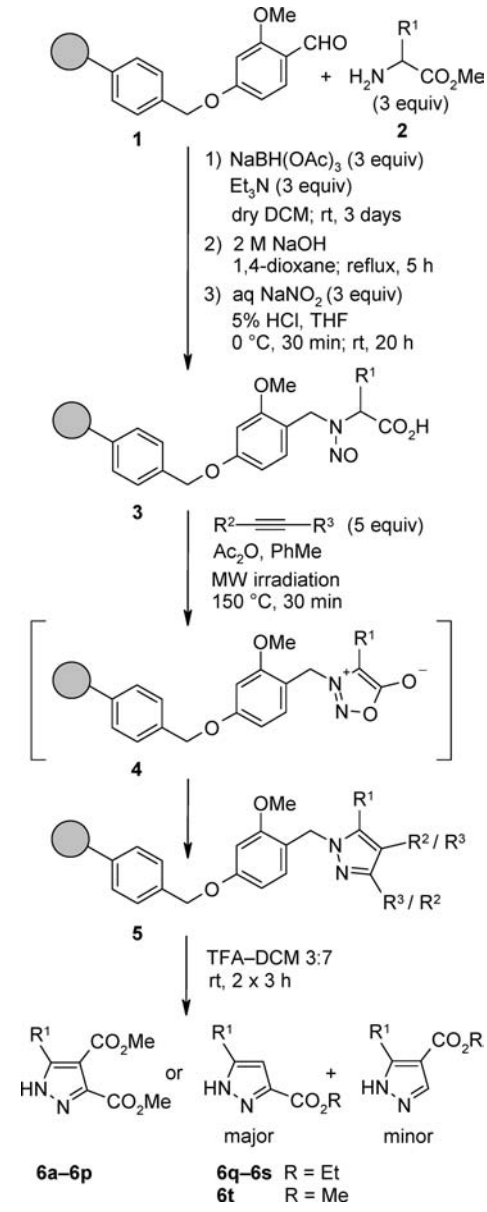
reviewed.[14] Solid-phase synthesis of pyrazoles has been studied mainly via hydrazine reactions[15] and also via 1,3-dipolar cycloadditions.[16] Acid-cleavable 2-methoxy-substituted resin has proven very useful in traceless solid-phase synthesis, and it has been utilized, e.g., in the synthesis of five-membered nitrogen heterocycles such as imidazoles,[17] 1,2,4-triazoles,[18] and 1,2,3-triazoles.[19] We now introduce a traceless solid-phase synthesis of *N*-unsubstituted pyrazole carboxylates via polymer-bound sydnones utilizing 2-methoxy resin. The resin protects the amino group during the *N*-nitrosation, and after the reaction steps the products are cleaved from the resin in a traceless manner yielding *N*-unsubstituted pyrazoles.

Several amino acid methyl esters were attached to formyl-functionalized Ameba resin **1** using a reductive amination (Scheme 1).[17,20] The amination, subsequent hydrolysis of the esters, and *N*-nitrosation were performed in a parallel fashion with the Radleys 12-place carousel reaction station. One-pot cycloaddition with dimethyl acetylenedicarboxylate, ethyl propiolate, or methyl propiolate under microwave irradiation in the presence of a water-removing agent gave polymer-bound pyrazoles **5**. The products **6** were cleaved from the resin with trifluoroacetic acid in a parallel fashion by shaking at room temperature in sealed syringes.

The purity of the crude pyrazoles was analyzed by LC-MS and ^{1}H NMR. Most of the crude products were obtained in high purities. The reactions were monitored with FT-IR and LC-MS. After the reactions, major changes in the FT-IR spectra were in the carbonyl area. Disappearance of the aldehyde band (1674 cm^{-1}) indicated successful attachment of the amino acid methyl ester, and hydrolyzed methyl esters (1725−1735 cm^{-1}) were detected as sodium salts of the acids (1580−1600 cm^{-1}). *N*-Nitrosation and 1,3-dipolar cycloaddition caused also changes in the carbonyl area and additionally some minor changes in FT-IR spectra. After the cleavage, analysis of the residual resins showed only traces of the peaks typical for these products; instead we detected a trifluoroacetate band (1780 cm^{-1}). LC-MS analyses gave further information about the reactions. The intermediate resins were first treated with TFA-DCM, and the cleaved compounds were then analyzed with LC-MS. Resin-bound amino acid ester and amino acid were cleaved in minor amounts coupled with the 4-hydroxy-2-methoxybenzyl linker. Cycloadditions were carried out under microwave irradiation at 150 °C for 30 min. Crude pyrazoles were obtained in small amounts and low purity at a reduced temperature (130 °C, 30 min). Continuing the reaction for 30 min at 150 °C, we obtained a high yield and crude product purity (>80%). When *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) was used as a dehydrating agent, instead of acetic anhydride, the crude product purity was under

Scheme 1. Solid-Phase Synthesis of Pyrazoles **6**



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50%. Interestingly, no signs of the 4-hydroxy-2-methoxybenzyl group could be seen attached to the crude pyrazoles cleaved from the resin, meaning traceless cleavage of the products. When ethyl or methyl propiolate was used in the cycloaddition reaction, instead of dimethyl acetylenedicarboxylate (DMAD), we obtained inseparable mixtures of regioisomers. The major regioisomer proved to be 3-carboxylic ester, and 4-carboxylic esters were obtained in minor amounts (~20−30% in crude products). Alkynes with electron-withdrawing groups were the most reactive in the cycloaddition, and under the same reaction conditions less activated alkynes such as ethyl phenylpropiolate gave only traces of the cycloadduct.

Regiochemistry of the reaction was studied with NMR analyses. In the major product (3-carboxylate), aromatic pyrazole proton C*H* appeared at 6.60−6.67 ppm, whereas in the other regioisomer (4-carboxylate) the aromatic proton was located at 7.98−8.03 ppm. This is consistent with the literature data.[21] Additionally, NOESY experiments confirmed the regiochemistry showing couplings through space between alkyl protons of R^1 and the aromatic pyrazole C*H* proton, proving that the pyrazole proton is in close proximity to the alkyl substituent. The obtained products, yields, and purities are listed in Table 1.

In conclusion, we have developed a convenient, novel method to synthesize *N*-unsubstituted pyrazoles on a solid support. A variety of substituents were introduced into the pyrazole ring. Widely available amino acids gave a good diversity of alkyl substituents and other functional groups in the pyrazole ring. The average yield per reaction step was over 80%. This method gives a facile approach to *N*-unsubstituted pyrazole carboxylates, starting from primary amino acid methyl esters, and the products can be utilized as building blocks for further reactions.

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Table 1. Yields and Purities of Pyrazoles **6a−t**

product	R^1	yield[a] (%)	purity[b] (%)
6a	hydrogen	32	>98
6b	methyl	54	>98
6c	ethyl	60	>95
6d	propyl	57	>95
6e	1-methylethyl	53	>98
6f	butyl	59	>90
6g	1-methylpropyl	53	>98
6h	2-methylpropyl	47	>98
6i	cyclohexylmethyl	57	>90
6j	benzyl	43	>90
6k	4-nitrobenzyl	17	>90
6l	4-benzyloxybenzyl	57	>90
6m	benzyloxymethyl	17	>80
6n	benzylsulfanylmethyl	12	>90
6o	2-methylsulfanylethyl	28	>80
6p	4-benzyloxycarbonylaminobutyl	23	>90
6q	1-methylethyl	24 (6:1)[c]	>98
6r	2-methylpropyl	23 (4:1)[c]	>95
6s	2-methylsulfanylethyl	14 (4:1)[c]	>98
6t	2-methylpropyl	18 (19:1)[c]	>98

[a] Overall isolated yields are based on the theoretically corrected loadings (0.83−1.04 mmol/g). [b] The purities were evaluated on the basis of analytical data. [c] The ratio of the regioisomers after chromatographic purification was evaluated on the basis of ^{1}H NMR.

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Supporting Information Available: General 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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