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LETTERS

Cascade and Sequential Palladium Catalysed Cyclisation-Azide Capture-1,3-Dipolar Cycloaddition Route to Complex Triazoles.

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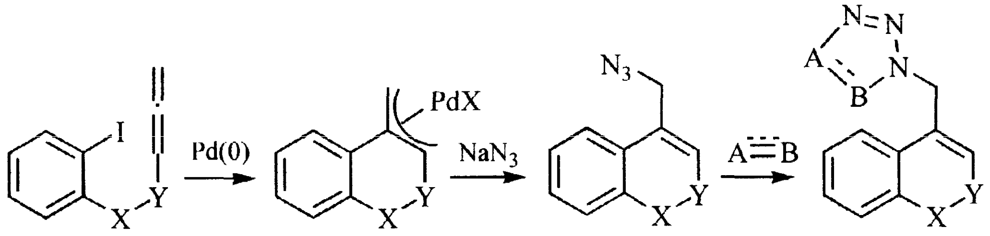
Abstract: Palladium catalysed processes involving sequential cyclisation of aryl iodides onto proximate allenes with capture by NaN_3 (and NaO_2SPh) followed by a 1,3-dipolar cycloaddition reaction utilizing DMAD, methyl propiolate and norbornadiene are described. When utilising the latter, the sequence can be carried out as a one-pot protocol which terminates with a retro Diels-Alder reaction.

There is a growing awareness that allenes constitute underutilized and versatile substrates for palladium catalysed processes and we[1] and others[2] have begun exploring their chemistry in both cyclisation and cycloaddition processes.

In this communication we describe sequential reactions involving palladium catalysed cyclisation of aryl iodides onto the centre carbon of proximate allenes and anion capture of the resulting π-allylpalladium(II) species by sodium azide followed by a 1,3-dipolar cycloaddition as depicted in Scheme 1. These two types of reaction provide a series of opportunities for linking two disparate ring forming reactions in novel sequential or cascade Tactical Combinations which potentially offer highly efficient and selective protocols. Such protocols can provide one-pot access to target molecules possessing a high degree of complexity which would otherwise require technically demanding multistep syntheses.



Scheme 1

A series of sequential reactions were explored first utilising dimethyl acetylenedicarboxylate (DMAD) as the dipolarophile in the cycloaddition step. Thus allenes (1), (4) and (7) react (DMF, RT, 12h) with sodium

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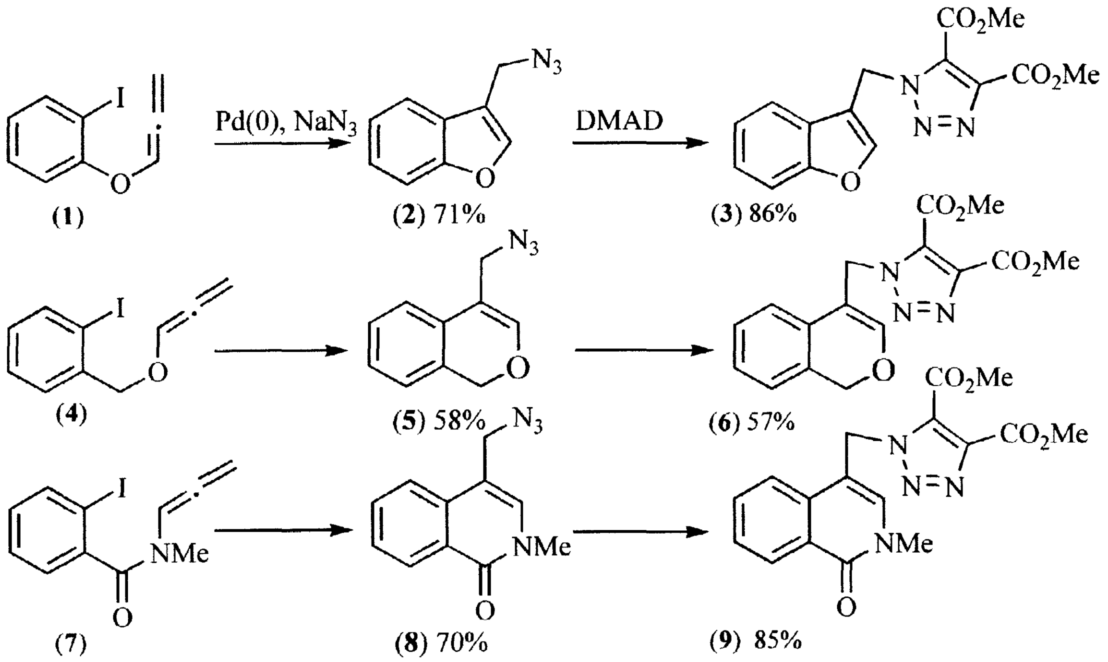
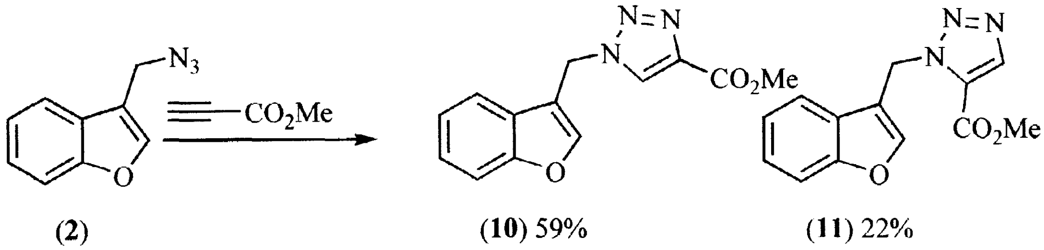
azide (2eq) in the presence of 10mol% Pd(PPh$_3$)$_4$ to afford regioselectively the azides (2), (5) and (8) respectively. The latter were then treated (PhH, reflux, 12h) with DMAD (1eq) to give the respective triazoles (3), (6) and (9).

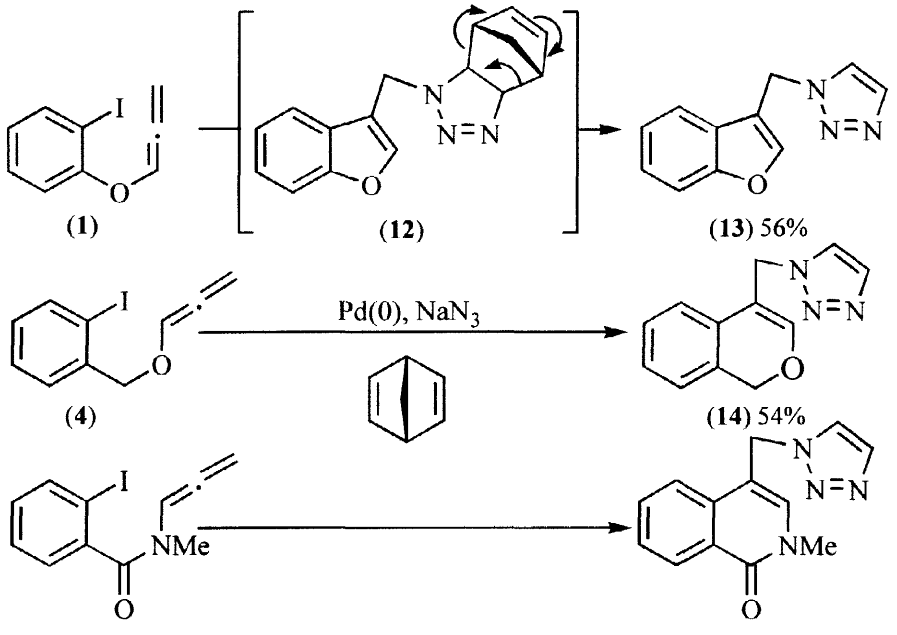


Under analogous conditions, reaction with methyl propiolate led to mixtures of cycloadducts (10) and (11), the major regioisomer being the 1,4-product (10). As expected[3] the regiochemistry was established from n.O.e. experiments.



It has not proved possible thus far to combine the sequential reactions using acetylenes as dipolarophiles into cascades. This is thought to be due to PPh$_3$ ligands reacting with acetylenes, thus shutting down the 1,3-dipolar cycloaddition reaction. Literature precedent[4] exists for this type of reaction.

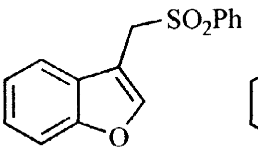
One-pot combination cascades were next explored using norbornadiene as the dipolarophile. Thus allenes (1), (4) and (7) react (DMF, 80-120 °C, 12h) with sodium azide (2eq) and norbornadiene (3eq) in the presence of 10mol% Pd(PPh$_3$)$_4$ to afford the triazoles (13), (14) and (15) in moderate yield *via* fragmentation of the initial cycloadduct e.g. (12, arrows). The intermediate cycloadducts were not detected under our reaction conditions. The facile retro Diels-Alder reaction[5] of the triazoline cycloadducts such as (12) reflects the incipient aromaticity in the retro Diels-Alder transition states. These cascades result in the formation of four new bonds and two rings and constitute termolecular queuing processes.



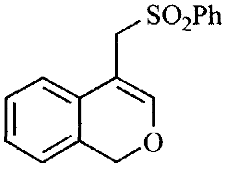
(7)

(15) 52%

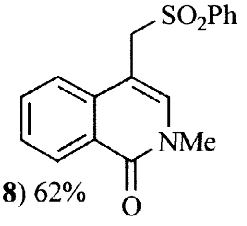
A similar anion capture process with allenes (1), (4) and (7) was achieved using sodium benzene sulphinate. Thus, the allenes react (DMF, RT, 12h) with sodium benzene sulphinate (2eq) in the presence of 10mol% Pd(PPh$_3$)$_4$ to afford the products (16), (17) and (18) regioselectively.



(16) 64%



(17) 55%



(18) 62%

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