Palladium catalyzed ring opening of furans as a route to α,β-unsaturated aldehydes†

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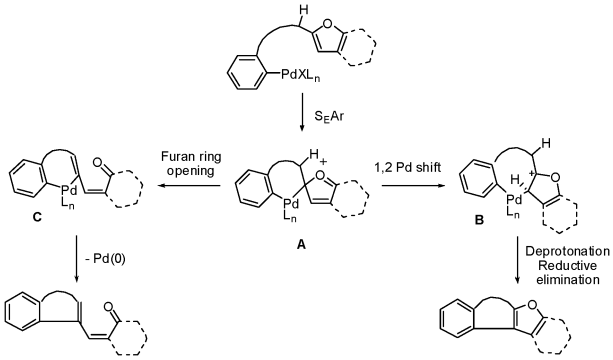
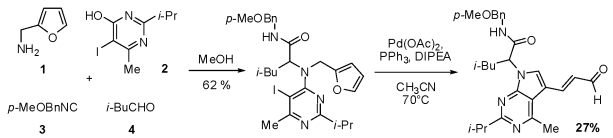
Furans may be ring opened *via* pallado-catalyzed reactions leading to α,β-unsaturated aldehydes and ketones tethered to indole and isoquinoline moieties. Besides their synthetic interest, these fragmentations bring interesting elements into the discussion around the reaction mechanisms involved in palladium C–H activations of electron-rich heterocycles.

With a Dewar resonance energy of 4.3 kcal mol^{-1}, furans represent the least stabilized among the classical five- and six-membered ring aromatic heterocycles.[1] This property may be illustrated by the different behavior of 5-membered ring heteroaromatics as dienes in Diels–Alder reactions as well as various ring opening reactions observed with furans.[2] The cleavage of the furan ring with strong Brønsted acids to form diketone derivatives has been known for many years.[3] In these reactions, the intermediate protonated furans may be trapped by internal nucleophiles to afford various heterocyclic systems.[4] The most powerful synthetic routes involving electrophilic activation of furan towards ring opening are certainly those involving oxidative conditions (such as the Achmatowicz reaction).[5] Considering all these ring opening reactions triggered by an electrophilic attack on furans,[6] one may be surprised by the absence of related fragmentations using electron deficient organometallic derivatives such as palladium(II) species.[7] The formation of aryl–aryl bonds through palladium catalyzed C–H activation of aromatic derivatives has recently been the object of tremendous efforts.[8] Studies on the C–H functionalization of furans have shown that both inter and intramolecular additions could be observed, with the 2-position being the most reactive.[9] When substituted at the 2-position, intramolecular couplings of furans usually lead to adducts functionalized at C-3. Among the various mechanisms proposed for these reactions,[10] we surmised that if an electrophilic pathway could be operative, reactive palladium intermediates could undergo ring opening of the furan moiety instead of the C-3 functionalization (Scheme 1).

In order to examine such transformations, we decided to prepare potential substrates using our 4-component Ugi–Smiles procedure with furfurylamines and *o*-iodohydroxyaromatic derivatives.[11] Compared with the preparation of model compounds using standard acylation/alkylation strategies, this procedure offers suitable starting materials in one step. Thus furan **5a** was prepared in 62% isolated yield from



Scheme 1 Potential C-3 functionalization/furan ring openings competition.



Scheme 2 Furan ring opening of Ugi–Smiles adduct **5a**.

furfurylamine **1**, iodopyrimidine **2**, isocyanide **3** and aldehyde **4** (Scheme 2). When **5a** was treated in acetonitrile with palladium acetate, triphenylphosphine couple and diisopropylethylamine (DIPEA), we were delighted to observe the formation of the pyrrolopyrimidine **6a** in a modest 27% yield (Scheme 2).

The conversion of **5a** into **6a** was then optimized using different bases, solvents and catalysts under both thermal and microwave conditions. The use of $PdCl_2(PPh_3)_2$ in hot acetonitrile gave a slightly higher yield of **6a** (40%) which could be improved to 85% by performing the reaction under microwave irradiation (130 °C, 100 W).

Under these conditions, a set of Ugi–Smiles adducts obtained from iodopyrimidines (Table 1, entries 1–8) and iodonitrophenols (Table 1, entries 9 and 10) can be transformed into the expected pyrrolopyrimidines and indoles in good to moderate yields.[12] Furans substituted at the 5 position afford α,β-unsaturated ketones instead of aldehydes in comparable yields (Table 1, entries 5–8). More interestingly, the scope of this reaction can be broadened as shown by the behavior of model compounds prepared by standard amination/alkylation procedures (Table 2).

Considering the various reports on palladium-triggered cyclizations onto furans, it is surprising that such a behavior has not been previously observed. This is probably due to the fact that the substrates examined lack a hydrogen capable of inducing fragmentation (hydrogen highlighted in intermediate **A**, Scheme 1)[9a–c] or the use of benzofurans, which are reluctant

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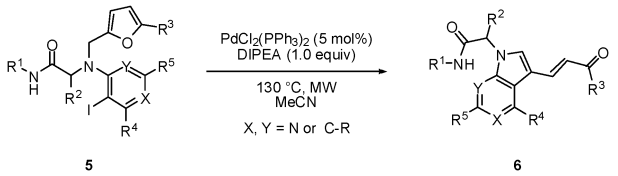
† Electronic supplementary information (ESI) available: Full characterisation for **5a-j**, **6a-j**, **7a-i**, **8a-I**, **9a-d** and **10a-d**. See DOI: 10.1039/c0cc04164e

Table 1 Palladium catalyzed furan fragmentation of Ugi–Smiles adducts



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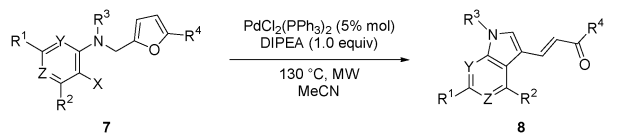
Entry	R^1	R^2	R^3	R^4	R^5	X	Y	Product (yield, %)
1	*p*-MeOBn	*i*-Bu	H	Me	*i*-Pr	N	N	**6a** (85)
2	*p*-ClBn	Me	H	Me	*i*-Pr	N	N	**6b** (88)
3	*p*-ClBn	H	H	Me	*i*-Pr	N	N	**6c** (68)
4	$CH_2CH_2Ar^a$	Me	H	Me	*i*-Pr	N	N	**6d** (71)
5	*p*-MeOBn	*i*-Bu	Me	Me	*i*-Pr	N	N	**6e** (76)
6	Cy	*i*-Bu	Me	Me	*i*-Pr	N	N	**6f** (58)
7	*p*-ClBn	*p*-ClPh	Me	Me	*i*-Pr	N	N	**6g** (66)
8	*p*-ClBn	*i*-Bu	Me	Me	Ph	N	N	**6h** (78)
9	*p*-MeOBn	Me	H	H	H	C–Me	$C–NO_2$	**6i** (66)
10	*p*-ClBn	*i*-Bu	H	H	H	C–Cl	$C–NO_2$	**6j** (71)

[a] Ar = 3,4-$MeOC_6H_3$

Table 2 Palladium catalyzed furan fragmentation of model compounds



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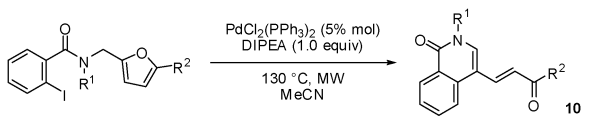
Entry	R^1	R^2	R^3	R^4	X	Y	Z	Product (yield, %)
1	*i*-Pr	Me	Et	H	I	N	N	**8a** (72)
2	*i*-Pr	Me	Me	Me	I	N	N	**8b** (77)
3	Ph	Me	Et	H	I	N	N	**8c** (76)
4	Ph	Me	Me	Me	I	N	N	**8d** (81)
5	Ph	Me	Bn	H	I	N	N	**8e** (75)
6	*i*-Pr	Me	Me	H	Br	N	N	**8f** (59)
7	H	H	Et	H	I	C–H	C–H	**8g** (83)
8	H	H	Bn	H	I	C–H	C–H	**8h** (78)
9	Cl	H	Me	H	I	C–H	C–H	**8i** (77)

to form highly reactive methylenequinone intermediates (corresponding to **C** in Scheme 1).[9d]

The examples reported in Table 1 and 2 underscore the high potential of this process for the preparation of indoles. These compounds are important medicinal scaffolds and the additional unsaturated carbonyl moiety opens up many opportunities for further functionalizations. In addition, this process is not limited to cyclizations forming five membered rings as shown by the behavior of furans **9**. Indeed, under similar treatment with palladium under microwave irradiation we could observe an analogous cascade leading to the formation of isoquinolinones **10** (Scheme 3).



9 10

10a: R^1=Et, R^2=H, 56% **10c**: R^1=Et, R^2=Me, 74%
10b: R^1=Ph, R^2=H, 52% **10d**: R^1=Ph, R^2=Me, 80%

Scheme 3 Furan ring openings towards isoquinolines.

Beside the synthetic potential of these fragmentations, the disclosure of this new reactive path reveals interesting mechanistic elements about palladium catalyzed C–H activation of heterocycles. Of the various mechanisms proposed for these reactions, Heck-type reactive pathways are usually discarded[10,13] and there are still discussions between electrophilic palladations (S_EAr path)[10a,b] and concerted metalation deprotonation processes (CMD path).[10c–e] In the case of 2-substituted furans, the fragmentations reported herein are in strong support of an S_EAr process. The mechanism of these reactions as well as their extension to other 5-membered ring systems are currently being examined.

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12 To a 0.25 M solution of the aniline **7g** (56 mg, 0.17 mmol) in acetonitrile were successfully added bis(triphenylphosphine)-palladium chloride (6 mg, 5 mol%) and diisopropylethylamine (30 μL, 0.17 mmol, 1 equiv.). The resulting mixture was then stirred under microwave activation for 20 min at 130 °C (power = 100 W, pressure = 13 bar). The crude mixture was first filtered and rinsed with methanol. After removal of the volatile materials, purification by flash chromatography (petroleum ether–diethyl ether, 50 : 50) gave **8g** (28 mg, 83%) as a white solid. Mp 99–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 15.7 Hz, 1H), 7.52 (s, 1H), 7.41 (d, J = 7.7 Hz, 1H), 7.37–7.27 (m, 2H), 6.74 (dd, J = 15.7, 7.9 Hz, 1H), 4.22 (q, J = 7.3 Hz, 2H), 1.53 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 194.1, 146.5, 137.4, 132.4, 126.1, 124.1, 123.3, 121.9, 120.6, 112.5, 110.2, 41.6, 15.2. IR (thin film) 1663, 1611, 1521, 1388 cm^{-1}. HRMS calculated for $C_{13}H_{13}NO$ 199.0997, found 199.0991.

13 Even though Heck type mechanisms are usually discarded, an alternative reaction pathway may involve, in our case, a carbo-palladation followed by a fragmentation to a π-allyl species and final reductive elimination.