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ARTICLE

Microwave-assisted Palladium catalysed C-H acylation with aldehydes. Synthesis and diversification of 3-acylthiophenes

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The use of MW allows the efficient palladium(II)-catalysed C-3 acylation of thiophenes with aldehydes *via* C(sp^2)-H activation for the synthesis of (cyclo)alkyl/aryl thienyl ketones (43 examples). Compared to standard thermal conditions, the use of MW reduces the reaction time (15 to 30 min *vs*. 1 to 3 hours), leading to improved yields of the ketones (up to 92%). Control of positional selectivity is achieved by 2-pyridinyl and 2-pyrimidyl *ortho*-directing groups at C-2 of the thiophene scaffold. To show the synthetic applicability, selected ketones were subjected to further transformations, including intramolecular reactions to directly embed the directing-group in the core-structure of the new molecule

Introduction

Thiophene scaffold is found in natural products, pharmaceuticals and other bioactive organic molecules, as well as in functional organic materials.[1] The regioselective acylation of thiophene has attracted the interest of synthetic chemists, because it gives access to biologically active (hetero)aryl and/or cycloalkyl thiophenyl methanones, such as anti-inflammatory drug (NSAID) suprofen[2] and tiaprofenic acid, diuretic tienilic acid[3] or anticancer and antiestrogenic Raloxifene,[4] which is being investigated as a treatment option for viral infections as SARS-CoV-2 (Figure 1).[5] The (hetero)aryl thiophenyl methanones can also be intermediates in the synthesis of optoelectronic materials.[6] Traditional methods to acylate thiophenes mainly rely on the classical Friedel–Crafts acylation reaction[7] of (hetero)arenes, where the regioselectivity is controlled by the electronic properties of the substrate.[8] Addition of aryllithium compounds to carboxylic acid derivatives[9] and carbonylative cross-couplings[10] from prefunctionalised heteroarenes also constitute two efficient alternative methods to prepare acylthiophenes. However, the environmental problems related to producing strong acidic- or salt-waste are important drawbacks of these procedures. In the last years, cross-dehydrogenative coupling (CDC) has become one of the most direct and efficient synthetic methods of C–C bond formation.[11] In this context, transition-metal-catalysed direct C-H activation/acylation of (hetero)arenes has revealed as an excellent tool for the synthesis of di(hetero)aryl ketones in an atom-economical way.[12] Positional selectivity is commonly controlled by directing groups, σ-chelating groups that contain Lewis basic heteroatoms, which are able to coordinate to the metal centre approaching it to a specific C-H bond. Ideally, these directing groups should be easily removed or incorporated in the final molecule.[13] In the absence of directing groups, selectivity problems can arise due to the inherent reactivity of the substrates. Thus, 2-acylthiophenes have been synthetized through palladium-catalysed direct addition of 2-subtituted thiophenes to nitriles. The acylation reaction proceeded well under the $Pd(OAc)_2$/2,2'-bipyridine system using D-(+)-camphorsulfonic acid as additive, although selectivity problems arose when starting from 3-substituted thiophenes, as the reaction takes place under substrate control.[14] To date, the C-H acylation of thiophene at the C-3 or C-2 position has been achieved by transition metal catalysis via C(sp^2)-H bond activation, using directing groups (e.g. pyridine, pyrimidine) to control site selectivity. For example, a ruthenium or rhodium-catalysed carbonylation of 2- and/or 3-pyridinylthiophene with CO and ethylene (toluene, 160 °C) resulted in propionylation at an *ortho* C-H bond.[15] Ruthenium-catalysed carbonylation reactions of thiophene with aryl iodides[16] or styrenes[17] have been developed by Beller. The three-component coupling processes proceeded with moderate to good yield in water using both pyridinyl and pyrimidinyl *ortho*-directing groups, but also working at high temperatures (up to 130ºC) and pressure (3 MPa) for long reaction times (20-24 h) (Scheme 1).

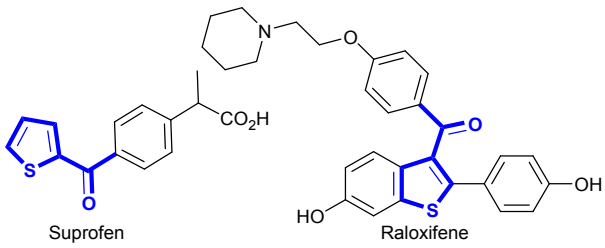

Figure 1. Examples of marketed drugs containing acylthiophene nucleus

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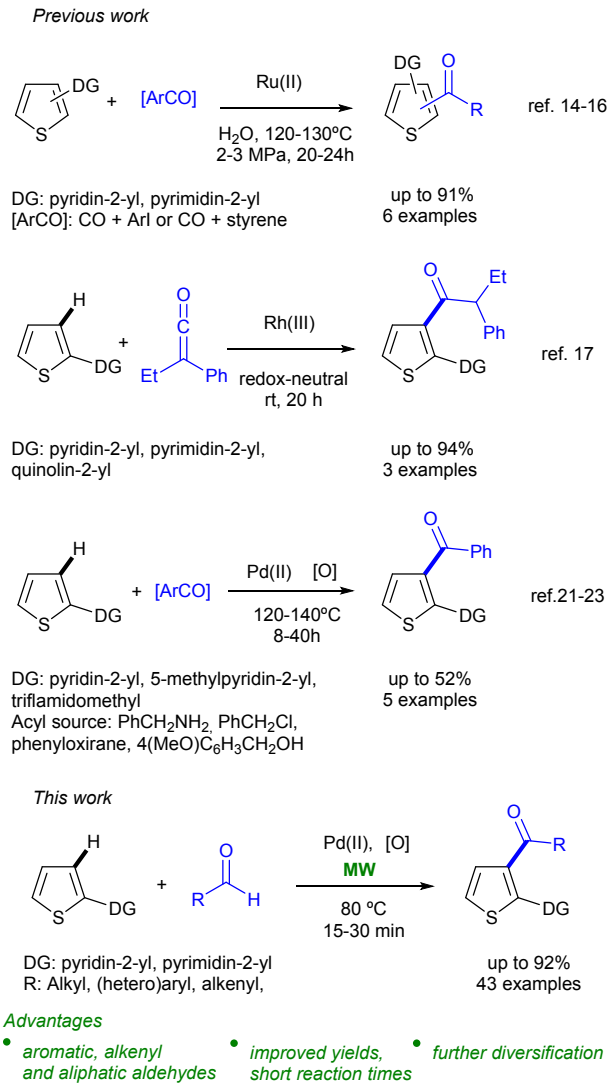
Electronic Supplementary Information (ESI) available: Synthesis and characterization data for compounds **1**-**12**. Additional assays on substrates **1a,b** with selected aldehydes **2** at different reaction times. X-ray diffraction data for **12a**. Copies of ^{1}H and ^{13}C NMR spectra of compounds **1**-**12**. See DOI: 10.1039/x0xx00000x

Li *et al*. [18] have developed the first Rh(III)-catalysed mild acylation of both C(sp^3)–H bonds and C(sp^2)–H bonds under redox-neutral conditions, using ketene as acylation reagent, which was successfully applied to the C-3 acylation of thiophene. Palladium (II)-catalysis has enabled significant progress in C(sp^2)-H bond acylation reactions of arenes in the presence of an oxidant. After the seminal works on Pd(II)-catalysed acylation of arenes with aldehydes using 2-pyridinyl as directing group,[19] the procedure has been applied using different acyl sources (aldehydes, α-oxocarboxylic acids, alcohols or toluene derivatives) and directing groups for the metalation (pyridines, pyrimidines, quinolones, etc.).[20] In this context, we have recently reported[21] the Pd(II)-catalysed C-2 acylation of pyrrole with aromatic and heteroaromatic aldehydes in the presence of an oxidant (TBHP) for the synthesis of di(hetero)aryl ketones. The use of 2-pyrimidine as directing group leads to 2-acylpyrroles in moderate to good yields, although diacylation could not be completely avoided. Nevertheless, when using 3-methyl-2-pyrydine as directing group, 2-acylpyrroles were selectively obtained. On the contrary, C-H acylation of thiophenes has been scarcely studied and limited to a few examples using 2-pyridinyl as directing group with benzylamine or benzyl chloride,[22] as well as phenyloxirane[23] as acylating agents. In all cases, low moderate yields (up to 52%) were obtained under rather harsh reaction conditions (120-140 ºC, 8-12h). A related procedure[24] using the triflamidomethyl as directing groups with a benzyl alcohol as acyl source required even longer reaction times (40h) to access the benzoylated thiophene in low yield (30%) (Scheme 1).

The efficiency of microwave (MW) irradiation in accelerating transition metal-catalysed homogeneous cross-coupling reactions (Heck, Suzuki, Sonogashira, Stille, Negishi, etc.) has been recognized for years.[25] More recently, it has been proven that MW heating can also help to develop new, safe, and energy efficient C-C and C-X bond forming C- H activation reactions, as illustrated in Van der Eycken's group work. Thus, they have developed MW-assisted: a) copper-catalysed oxidative cyclisation of acrylamides with non-activated ketones; b) ruthenium-catalysed *ortho*-C-H functionalization of *N*-benzoyl-α-amino ester derivatives; c) rhodium(III)-catalysed annulation via C(sp^2)-H activation.[26] However, the effect of MW irradiation on palladium catalysed radical C-H acylation reactions has not been studied. Herein we report the first example of a microwave-assisted selective palladium(II)-catalysed C-3 acylation of thiophenes with aldehydes via C(sp^2)-H activation for the synthesis of (cyclo)alkyl/aryl thienyl ketones under mild conditions and in short reaction times (15 to 30 min), compared to standard thermal conditions. Control of positional selectivity is achieved by 2-pyridinyl and 2-pyrimidyl *ortho*-directing groups at C-2 of the thiophene scaffold. Diversification of these ketones illustrates the potential of the method, including intramolecular reactions to embed the directing-group in the core-structure of the new molecule (Scheme 1).



Scheme 1. Transition-metal-catalysed C–H acylation reactions on thiophenes

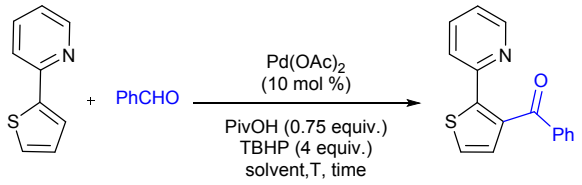
Results and discussion

We started studying the use of pyridine as directing group on C-2, in the reaction of **1a** with benzaldehyde (**2a**) and using TBHP as the oxidant, under the conditions previously optimised by our group for the acylation of pyrroles,[21] in toluene at 60 ºC using conventional heating and in the presence of pivalic acid as additive (Table 1, entry 1). Gratifyingly, full conversion of **1a** was observed after 2 hours and the expected ketone **3a** was isolated as the major compound with a good yield (78%), although the formation of decomposition products was also observed. A shorter reaction time (1 h), using a stoichiometric amount of PivOH led to a similar isolated yield of **3a**, although unreacted **1a** was also recovered (Table 1, entry 2). The reaction of **1a** was not complete at lower temperature (40 ºC) for a longer time (Table 1, entry 3).). However, the use of higher temperatures and longer reaction times led to decomposition products, significantly reducing the isolated yield of **3a** (Table 1, entries 4-5). A change in the solvent to DCE or chlorobenzene did not

improve the results, observing once again the formation of decomposition products that lowered the isolated yield of **3a** (Table 1, entries 6-8). The reaction could also be carried out in the absence of any added solvent (TBHP is used as a 5.5 M solution in decane) (Table 1, entry 9), and it is compatible also with the use of water as solvent (using in this case a TBHP water solution), although unreacted **1a** was recovered. The reactivity drops significantly when a surfactant is used (Table 1, entries 10-12). Toluene at 60 ºC was selected as the optimal solvent and temperature, and the reaction was tested with different aromatic aldehydes (Table 2). As it has been reported in related examples,[20] the structure of the aromatic aldehyde does not have a strong influence on the reactivity.

As shown in Table 2, generally higher reactivity is observed when the aromatic ring is substituted with electron-donating groups, what would lead more nucleophilic radical intermediates, but the reaction also works with electron-withdrawing substituents (Table 2, entries 1-6). 3-Furan-3-carbaldehyde **2h** could also be used, although it presented lower reactivity, obtaining **3h** in a moderate yield (Table 2, entry 7). The extension to aliphatic or α,β-unsaturated aldehydes **2i** and **2j** (Table 2, entries 8-9) is also possible, but they showed lower reactivity, recovering unreacted **1a**. However, if the reaction times were extended, decomposition of the products started to occur, lowering the isolated yields of ketones **3**. The examples shown in Tables 1 and 2 show that longer reaction times or higher temperatures led to decomposition instead of higher conversions, probably due to oxidation reactions of the thiophene ring.[3]

Table 1. Acylation of **1a** with benzaldehyde (**2a**) under thermal conditions

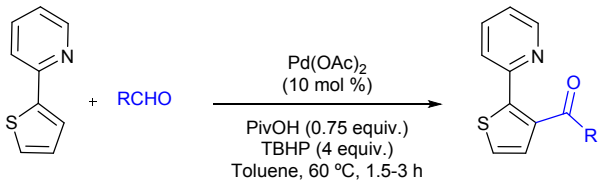


1a **2a** **3a**

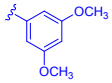
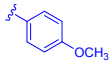
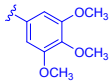
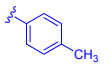
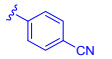
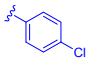
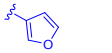
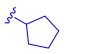
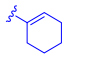
entry	Solvent	T (ºC)[a]	time (h)	3a (%)[b]
1	toluene	60	2	78
2	toluene	60	1	76[c,d]
3	toluene	40	3.5	57[c]
4	toluene	50	17	63
5	toluene	120	1.5	36
6	DCE	60	1.5	65
7	PhCl	60	1.5	74
8	PhCl	60	1	72
9	-	60	1.5	68
10	H_2O	60	2	61[c,e]
11	H_2O	60	2.5	19[c,e,f]
12	H_2O	20	24	17[c,e,f]

[a]The reactions were carried out with **1a** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol), **2** (1 mmol) and TBHP (2 mmol) in 10 mL sealed reaction tubes inserted in a heating block. The indicated temperature refers to the external temperature of the heating block. [b]Yield (%) of isolated pure compound. [c]Unreacted 1a was recovered. [d]1 equiv. of PivOH was used. [e]TBHP solution in water was used. [f] SDS (5%) was added

Table 2. Synthesis of 3-acyltiophenes **3b-j** under thermal conditions



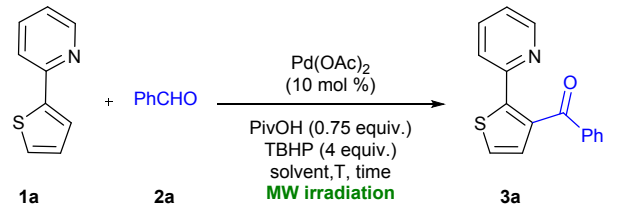
1a **2b-j** **3b-j**

entry	R	time (h)	3	Yield (%)[a]
1		1.5	**3b**	78
2		1.5	**3c**	57[b)]
3		1.5	**3d**	74
4		1.5	**3e**	78
5		2	**3f**	71[b]
6		1.5	**3g**	67
7		1.5	**3h**	47[b]
8		1.5	**3i**	45[b]
9		3	**3j**	53[b]

[a]The reactions were carried out with **1a** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol), **2** (1 mmol) and TBHP (2 mmol) in 10 mL sealed reaction tubes inserted in a heating block. Yield (%) of isolated pure compound. [b]Unreacted **1a** was recovered

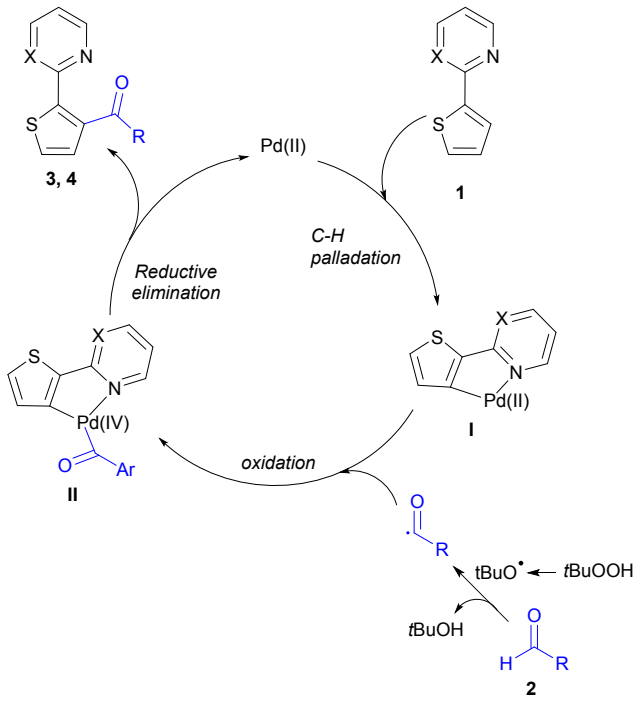
In view of these results, we decided to test the acylation reaction under MW irradiation assuming that an increase of the reaction rate, usually associated with the use of this technique,[25,26] would lead to shorter reaction times, preventing decomposition of the products and producing higher isolated yields of ketones **3**. We started using the same reaction conditions used for the thermal heating (toluene at 60ºC), checking the evolution of the reaction at different reaction times (Table 3, entries 1-3). Full conversion of the substrate **1a** was achieved only after 50 min, obtaining an improved 85% isolated yield of **3a**. No decomposition was observed, and unreacted **1a** was recovered with shorter reaction times (20 or 40 min). More polar solvents were checked, and it was found that water could be used at 60 ºC, but no full conversion was obtained after 40 min (Table 3, entries 4-5). A significant improvement was finally found using DCE at 80 ºC, which led to a 84% isolated yield of **3a** in only 15 min The yield was similar (80%) when the reaction was carried out in 1 mmol scale (Table 3, entry 6).

Table 3. MW-assisted acylation of **1a** with **2a**



	Solvent	T (ºC)[a]	time (min)	**3a** Yield (%)[b]
1	toluene	60	20	57[c]
2	toluene	60	40	67
3	toluene	60	50	85
4	H_2O	60	20	33[c]
5	H_2O	60	40	54[c]
6	DCE	80	15	84 (80)[d]
7	DCE[e]	80	15	42[c]
8	DCE[f]	80	15	58
9	DCE[g]	80	15	[c]
10	DCE[h]	80	15	[c]

[a]The reactions were carried out with **1a** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol), **2** (1 mmol) and TBHP (2 mmol) in 10 mL sealed reaction tubes. The indicated temperature, obtained using a maximum power of 200W, refers to the internal reaction temperature measured by an infrared sensor. [b]Yield (%) of isolated pure compound. [c]Unreacted **1a** was recovered. [d]Isolated yield obtained when the reaction was performed in 1 mmol scale. [e]No PivOH was used. [f]5 mol % of $Pd(OAc)_2$ was used. [g]No $Pd(OAc)_2$ was used. [h]No TBHP was used.



Scheme 2. Proposed schematic mechanism of C-3 acylation of thiophenes **1a,b**.

As shown before,[21] the use of pivalic acid was also important for reactivity, as the yield of **3a** dropped to 42% in its absence in the same time (Table 3, entry 7), as it was the catalyst loading used (Table 3, entry 8). Finally, it was also checked that both the palladium catalyst and the oxidant are required, as the reaction does not take place at all in their absence (Table 3, entries 9-10).

The generally accepted mechanism for this type of reactions is shown in Scheme 2. First, the chelation assisted C-H activation of **1a,b** to form palladacycle **I** would occur via a concerted metalation-deprotonation (CMD) mechanism, which would be the rate-determining step, as it has been demonstrated by DFT calculations and kinetic isotopic effects.[27] Subsequent oxidative addition of an acyl radical, generated from the aldehyde **2** via hydrogen abstraction by *t*-BuO· radical from the oxidant (TBHP), would led to a Pd(IV) intermediate **II**. Reductive elimination of **II** would allow C-C bond formation affording 3-acylthiophenes **3** and **4.**

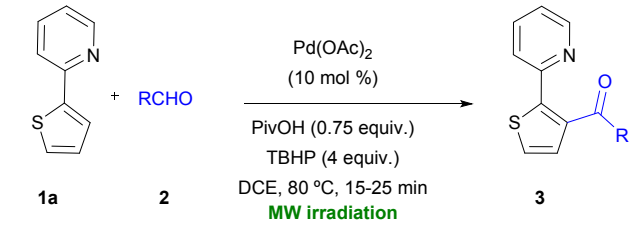
Next, we explored the substrate scope for aldehydes. The optimised reaction conditions were applied to a series of aromatic, heteroaromatic, aliphatic and alkenyl aldehydes, as shown in Table 4. Ketones **3b-3j** were obtained in generally good yields in 15-25 minutes, improving the results obtained under standard thermal conditions (Table 2), with the exception of **3c** and **3f** that gave only moderate yields and unreacted **1a** was also recovered. This acylation reaction was further extended for the synthesis of ketones **3k-3v**. Thus, a variety of aromatic aldehydes could be used, tolerating the presence of halogens or alkyl groups (**3k-3m**).

The reaction is less efficient when electron-withdrawing groups are introduced in the aromatic ring (**3f, 3o**), specially in the case of a nitro group (**3n**). Heteroaromatic or aliphatic aldehydes could also be used. Interestingly, the reaction is compatible with the use of more complex aldehydes, such as (*S*)-perylladehyde or (*R*)-myrtenal to obtain ketones **3r** and **3s** in moderate yields. However, adamantane-1-carbaldehyde (**2v**) showed a low reactivity, obtaining a low yield of **3v** (23%). Under these reaction conditions, the formation of decomposition products was completely avoided. However, full conversion of the starting thiophene could not be achieved, depending on the aldehyde used, and unreacted **1a** was recovered in some cases (Table 4).

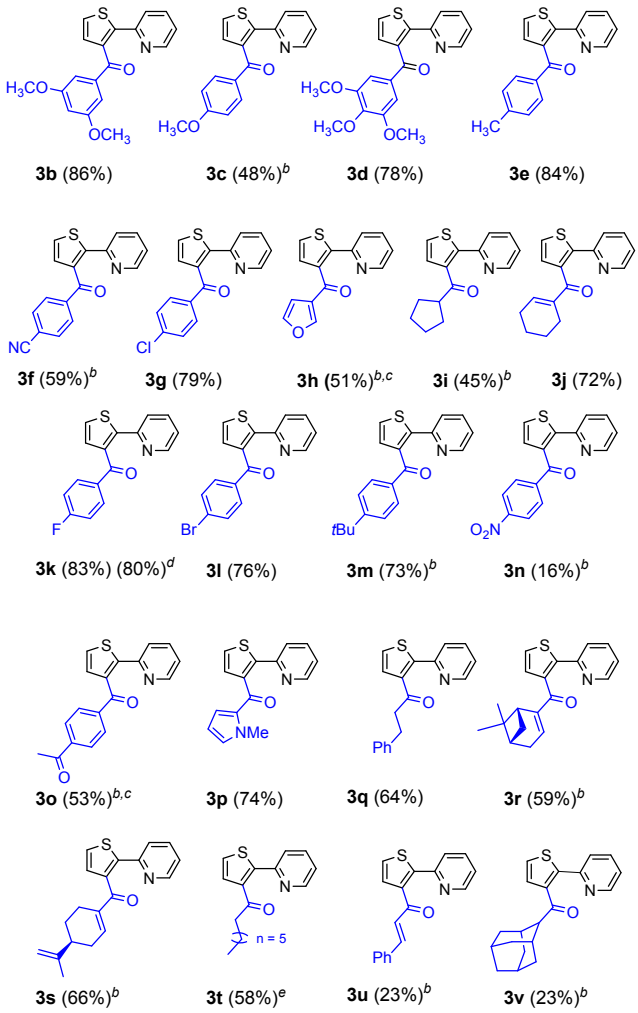
However, the extension of the reaction times at 80 ºC for these reactions did not improve the isolated yields of ketones **3**, as decomposition starts to be observed.

We next studied the efficiency of 2-pyrimidine as directing group for these reactions (Table 5). The reaction times could be extended to 20-30 min without decomposition of the products, and ketones **4** were obtained in general with comparable yields to those of ketones **3** (Table 4), although some remarkable improvements were achieved. For instance, ketone **4f** was obtained with an 84% yield *vs* 59% for **3f**. Compared to aromatic aldehydes, alkyl or alkenyl aldehydes gave in this case also lower yields of **4q-s**, due to recovery of unreacted **1b** (see Supplementary Information for additional essays using different reaction times). For comparison, selected examples (**4a-c**, **4e-f**, **4i**) were also carried out under standard thermal conditions, using toluene at 60 ºC for 1.3 hours.

Table 4. MW-assisted acylation of **1a** with aldehydes **2**[a]



1a **2** **3**

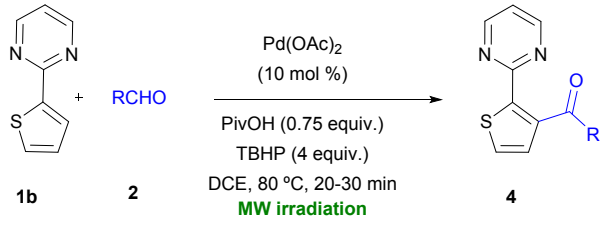


[a]Yield (%) of pure isolated product. The reactions were carried out with **1a** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol), **2** (1 mmol) and TBHP (2 mmol) in 10 mL sealed reaction tubes. The indicated temperature, obtained using a maximum power of 200W, refers to the internal reaction temperature measured by an infrared sensor [b]Unreacted **1a** was recovered. [c]15 mol% of catalyst was used. [d]Reaction done in 1 mmol scale. [e]Reaction done in 2 mmol scale.

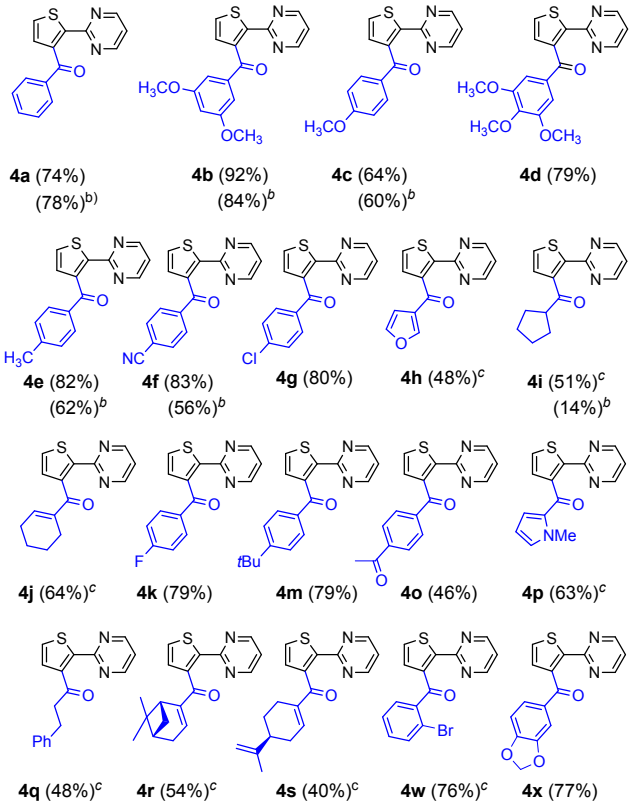
With the exception of **4a**, the yields were lower than those obtained under MW irradiation, especially in the cases of **4i** and **4f.**

The MW-assisted acylation reaction was tested also in different heterocyclic systems (Scheme 3). In the case of benzothiophenes **5a,b**, the performance of the pyridine as directing group for the C-2 acylation was clearly superior obtaining **6a** with a moderate yield (Scheme 3).

Table 5. MW-assisted acylation of **1b** with aldehydes **2**[a]

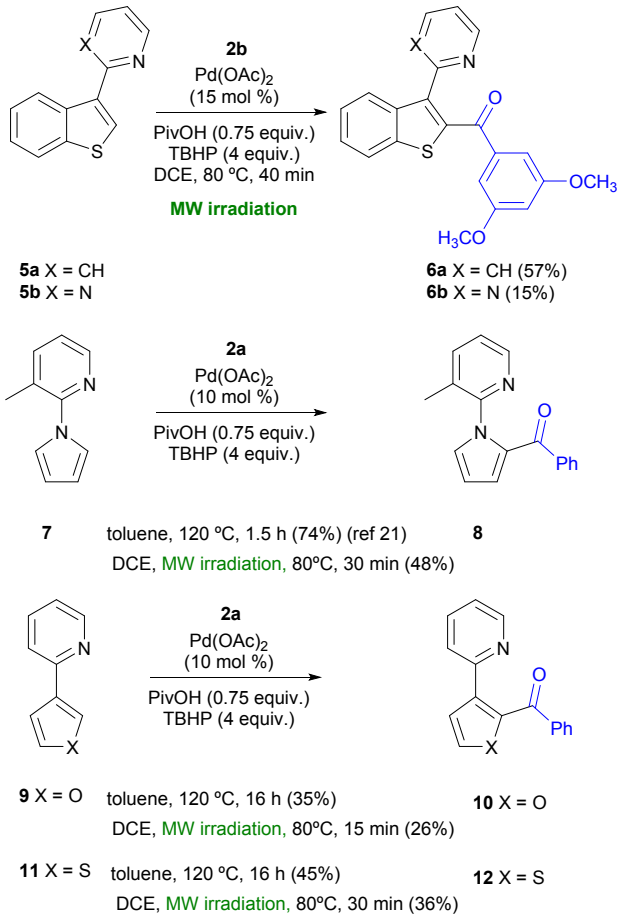


1b **2** **4**



[a]Yield (%) of pure isolated product. The reactions were carried out with **1b** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol), **2** (1 mmol) and TBHP (2 mmol) in 10 mL sealed reaction tubes. The indicated temperature, obtained using a maximum power of 200W, refers to the internal reaction temperature measured by an infrared sensor. [b]Yield (%) of pure compound when the reaction was carried out in toluene at 60 ºC, 1.3 h, with standard heating. [c]Unreacted **1b** was recovered.

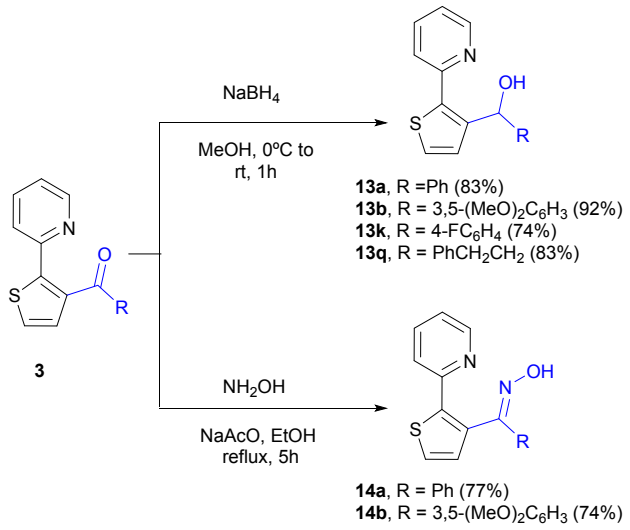
The reaction was applied also to pyrrole **7**, although in this case, the results previously obtained under thermal conditions (toluene, 120 ºC, 1.5 h, 74%)[21] could not be improved. The reaction under MW irradiation led to **8** in a 48% isolated yield, recovering unreacted pyrrole **7**. The C-2 acylation of furan **9** was also tested (Scheme 3). Under thermal conditions (toluene, 120 ºC) **10** was obtained regioselectively, although in a low yield (35%), mainly due to the formation of decomposition products. Unfortunately, this result could not be improved under MW irradiation conditions observing also decomposition. Besides, unreacted **9** was recovered, obtaining **10** in a 26% isolated yield after 15 min. A similar result was obtained for the C-2 acylation of thiophene **11**, obtaining **12** regioselectively but in low isolated yield, not improving the result obtained under thermal conditions.



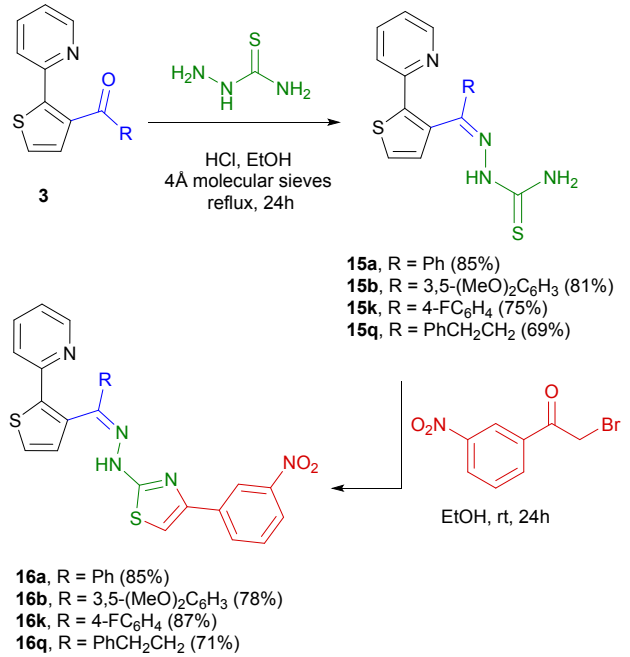
Scheme 3. Acylation of other heterocycles

The acyl thiophenes obtained provide a platform for a rich array of downstream manipulations. In this way, this approach enables relatively straightforward access to a variety of analogues that may present interesting applications. Thus, the versatile reactivity of the carbonyl group can used to perform reduction or other nucleophilic additions, as illustrated by a few representative examples shown in Scheme 4. Reduction of acyl thiophenes **3** with $NaBH_4$ under mild conditions provide access to compounds containing a benzylic functionality **13** [i.e. heteroaryl benzyl alcohol], which can be inhibitors of PI3K and/or VPS34, useful for treating proliferative, inflammatory, or cardiovascular disorders.[28] Besides, addition of hydroxylamine to acyl thiophenes **3** in the presence of NaOAc led to (*E*)-oximes **14** also in good yields. It has been recently reported that the presence of a thiophene moiety in pinane-derived oximes can be crucial for their anti-influenza activity.[1d]

In addition, the reaction of acyl thiophenes **3** with thiosemicarbazide in acid media (HCl, EtOH, reflux) furnished (*Z*)-thiosemicarbazones **15** in high yield (Scheme 5). This type of thiosemicarbazones are cathepsin L inhibitors (e.g. SSAA09E1), which may be a therapeutic option for COVID-19[29] because they can prevent the progression of pulmonary fibrosis.[30] They are also inhibitors of trypanosomal cathepsins rhodesain and TbcatB[31] and potential antileukemic agents.[32]



Scheme 4. Synthesis of heteroaryl phenyl alcohols **13** and (*E*)-oximes **14** from acylthiophenes **3**

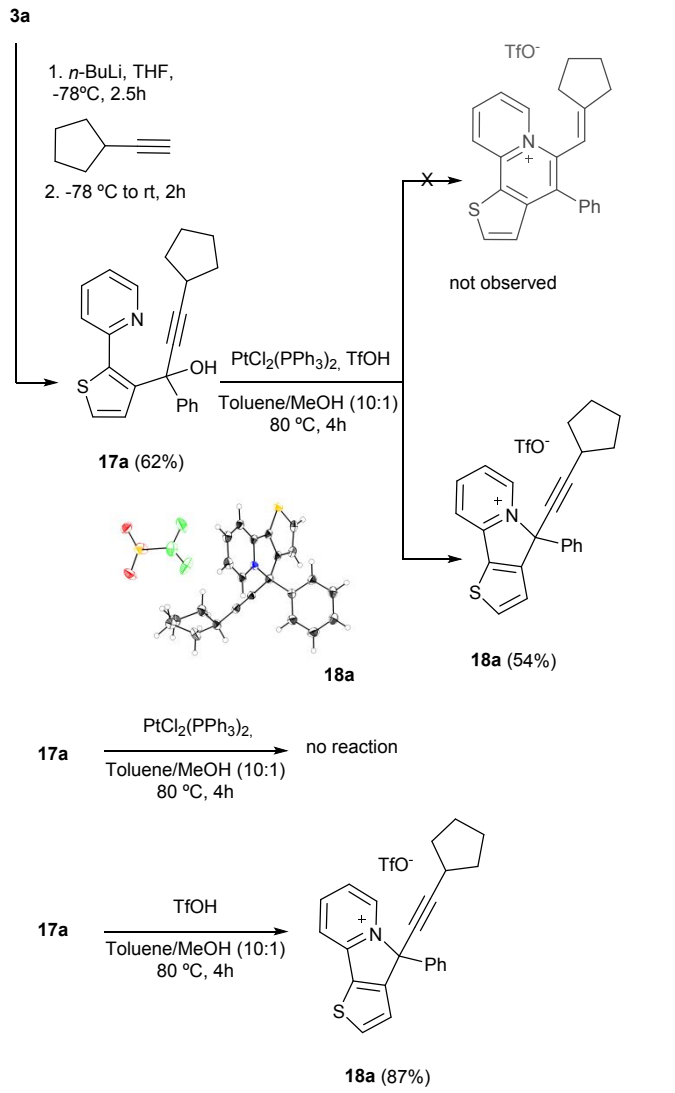


Scheme 5. Synthesis of thiosemicarbazones **15** and 4-(3-nitrophenyl)thiazol-2-ylhydrazones **16**

The obtained thiosemicarbazones **15** also served as good precursors to prepare more complex heterocycles, as illustrated with the synthesis of 4-(3-nitrophenyl)thiazol-2-ylhydrazones **16** by the Hantzsch reaction with 2-bromo-3'-nitroacetophenone (EtOH, rt) (Scheme 5). It should be noted that **16**-like thiazol-2-ylhydrazones have been proven promising antioxidants and selective hMAO-B inhibitors, so they are potential leads for the design of novel therapies for neurodegenerative disorders.[33]

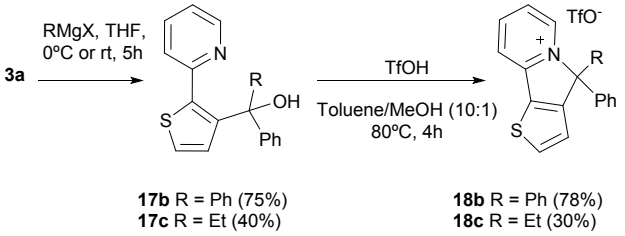
To expand the synthetic utility of the methodology, we decided to incorporate the directing group in the final coupled products. For this purpose, we selected a recently described Pt(II)-

catalysed intramolecular C–N bond formation between the pyridine nitrogen and metal-activated alkyne to access quinolizinium-type heteroaromatics.[34] Thus, addition of lithium cyclopentylacetylide, generated by deprotonation of cycopentylacetylene with *n*-BuLi at -78 ºC, to **3a** led to the formation of the tertiary alcohol **17a**. However, treatment of **17a** with $PtCl_2(PPh_3)_2$ in the presence of triflic acid led to the 4*H*-thieno[2,3-*a*]indolizin-5-ium salt **18a**, instead of the expected quinolizinium-type heteroaromatic. The structure of the indolizinium salt **18a** was unambiguously confirmed by X-ray analysis[35] (Scheme 6). The role of the acid in the formation of the quinolizinium salt would be to protonate the pyridine, which enables the alkyne to coordinate the platinum catalyst.[34] However, in our case the formation of **18a** would arise from intramolecular reaction of pyridine nitrogen with a stable tertiary benzylic carbocation, generated from the alcohol in the acidic reaction media. Control experiments were carried out with **17a**.



Scheme 6 Obtention of 4*H*-thieno[2,3-*a*]indolizin-5-ium salt **18a**

As expected, in the absence of acid, with the platinum catalyst, the reaction does not take place at all and unreacted **17a** was recovered after 3 h at 80 ºC. On the contrary, when the reaction was carried out just with triflic acid, in the absence of the platinum catalyst, **18a** was isolated in excellent yield (87%). This unprecedented fused heterocyclic structure could be considered as a thiophene analogue of pyridoisoindoles or pyridoisoindolium salts found in fluorescent materials and bioactive compounds, and recently obtained by molybdenum–catalysed cyclisation of analogous ketones,[36] and also present in more complex pyridoisoindolium structures used as fluorophores.[37] Intrigued by this reactivity, we extended this cyclisation to the tertiary diarylmethanol **17b** and alkyl aryl methanol **17c**, obtained by simple Grignard addition to ketone **3a** (Scheme 7) In both cases, the indolizinium salts could be obtained, although the low yield of **18c** probably is related to the ease of formation of the intermediate cations. In any case, the synthesis of thienoindolizinium salts **18** showcases a route to incorporate the directing group into the final product.

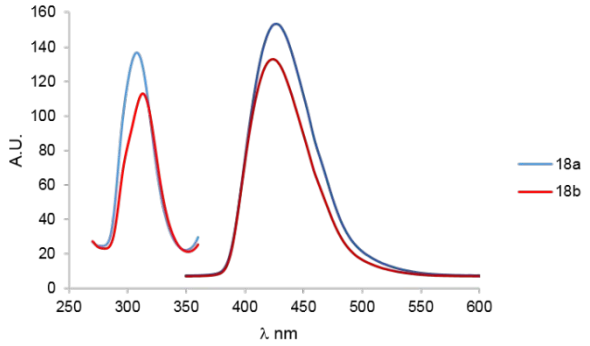


Scheme 7. Synthesis of 4*H*-thieno[2,3-*a*]indolizin-5-ium salts **18b,c**

These indolizinium salts exhibit fluorescent properties. Figure 2 depicts the UV–visible absorption and the fluorescence spectra of **18a** and **18b** in acetonitrile 1.15mM. Both salts **18a,b** showed similar absorption spectra (λ_{em} = 308-313 nm). The emission wavelengths are in the indigo region (λ_{em} = 424-427 nm) with high Stoke's shift values (>110), which could be interesting for potential biological applications[38] of these ionic fluorophores. The small differences on the absorption/emission wavelengths of both compounds reflects that there is not much influence of the nature of the substituent at the quaternary centre C-4 of the 4*H*-thieno[2,3-*a*]indolizin-5-ium moiety, as they are non-conjugated with the heterocyclic nucleus (see X-Ray structure of **18a** in Scheme 6). This is one of the few examples of ionic fluorophores with a quaternary pyridinium core.[37]

Conclusions

In conclusion, we have developed an efficient microwave-assisted palladium(II)-catalysed C-3 acylation of thiophenes with aldehydes. The reaction can be applied to aromatic, heteroaromatic, and also aliphatic aldehydes. The use of MW allows the obtention of ketones **3** and **4** in high yields at 80 ºC and in short reaction times (15 to 30 min), avoiding formation of decomposition products associated with longer reaction times required under standard thermal conditions. Further



	Compd	λ_{abs}[a] (nm)	λ_{em}[b] (nm)	ΔStoke[c] (nm)
1	**18a**	308	427	119
2	**18b**	313	424	111

[a]The maximum absorption wavelength in acetonitrile (1.15 mM). [b] Excited at the maximum absorption wavelength in acetonitrile (1.15 mM). [c]Stoke shift = $\lambda_{em} - \lambda_{abs}$.

Figure 2. Excitation and emission spectra of indolizinium salts **18a,b** at 1.15 mM in acetonitrile. Absorption and Emission maxima.

transformations of these ketones led to compounds with potential biological activities (e.g. thiazol-2-ylhydrazones) or to fluorescent 4*H*-thieno[2,3-*a*]indolizin-5-ium salts, in which the directing-group is embedded in the core-structure of the new molecule. The described methodology provides an improved procedure for C-H bond functionalization on thiophenes, with a high atom economy (99%), and would find broad utility in synthetic applications for the synthesis of complex target molecules.

Experimental Section

General methods.

Melting points were measured in unsealed capillary tubes. NMR spectra were obtained at 300 MHz for ^{1}H, at 75.5 MHz for ^{13}C, and at 282.4 MHz for ^{19}F using $CDCl_3$ as solvent at 20-25 ˚C, unless stated otherwise. DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC) were used when necessary for the assignments of individual ^{13}C and ^{1}H resonances. Electron impact (EI, 70 eV) or Electrospray ionization (ESI^+) sources were used for obtaining mass spectra. A TOF detector was employed for the obtention of exact mass. IR spectra were obtained using an ATR. Fluorescence spectra were measured using a Jasco FP-6500 spectrofluorimeter using acetonitrile as solvent at 1.15 mM. Emission spectra were acquired irradiating the sample at its maximum absorbance. Both, excitation and emission spectra were collected with an excitation-slit bandwidth of 1nm and an emission-slit bandwidth of 3 nm, and were recorded at 25 ºC. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was carried out on silica gel (230-400 mesh). All solvents used in reactions were purified according to standard procedures. $Pd(OAc)_2$ (98% purity) was purchased from Aldrich, and was used without further purification. Aldehydes **2** were commercially available. MW assisted reactions were carried out using a CEM Discover Lab Mate Reactor. The reaction temperature was measured by an integrated infrared sensor, and the reaction times indicated refer to the time at the given temperature. The maximum power supplied to reach the stated temperature was 200 W.

Acylation reactions of 1a,b with aldehydes. General procedure (thermal conditions).

Under argon atmosphere, a sealable reaction tube (10 mL, 1.3 × 9 cm) equipped with a stirring bar was charged with **1a,b** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol) and the corresponding aldehyde **2b-j** (1 mmol). After, toluene was added (1 mL), and the mixture was stirred for 2 min until solids were dissolved. Then, TBHP (5.5 M in decane, 2 mmol) was added, reaction tube was sealed and the reaction mixture was stirred at 60 °C for 1-3 h. After cooling to room temperature, the reaction mixture was filtered through silica gel and the filtrate was concentrated under vacuum. The residue was purified by column chromatography affording **3a-j**.

Microwave-assisted acylation reactions of 1a,b, 5a,b, 7, 9, and 11 with aldehydes. General procedure.

Under argon atmosphere, a sealable reaction tube (10 mL, 1.3 × 9 cm) equipped with a stirring bar was charged with **1a,b**, **5a,b**, **7, 9** or **11** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PivOH (0.38 mmol) and the corresponding aldehyde **2a-x** (1 mmol). After, DCE was added (1.5 mL), and the mixture was stirred for 2 min until solids were dissolved. Then, TBHP (5.5 M in decane, 2 mmol) was added; the reaction tube was sealed and heated under microwave irradiation at 80 °C for 15-30 min. After cooling to room temperature, the solvent was evaporated under vacuum and the residue was purified by column chromatography affording **3a-v, 4a-x**, **6a,b, 8**, **10** or **12**.

Author Contributions

N. Sotomayor and E. Lete conceptualized and supervised the project. N. Sotomayor and E. Lete wrote the original draft, reviewed, and edited the manuscript. C. Santiago did the major chemical experimental part and wrote the first experimental draft of ESI. X. Jiménez-Aberasturi and E. Lecea also participated in the chemical experimental work. M. G. Lete performed and wrote the fluorescence study. N. Sotomayor and E. Lete were responsible of funding acquisition. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

There are no conflicts to declare

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