Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
Status : Postprint (Author's version)

VERSATILE SYNTHESIS OF DISSYMMETRIC DIARYLIDENEACETONES VIA A PALLADIUM-CATALYZED COUPLING-ISOMERIZATION REACTION

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Abstract: As a twofold Michael system, the diarylideneacetone core is of particular interest in organic synthesis and for therapeutic applications. To overcome the drawbacks of the classical Claisen- Schmidt protocol, a new methodology for the synthesis of dissymmetric (hetero)diarylideneacetones has been developed. Conditions were optimized with a Box-Behnken design of experiment. The milder reaction conditions allow the efficient preparation of fluorinated, or heteroaromatic, dissymmetric diarylideneacetones which cannot be obtained through the classical Claisen-Schmidt protocol.

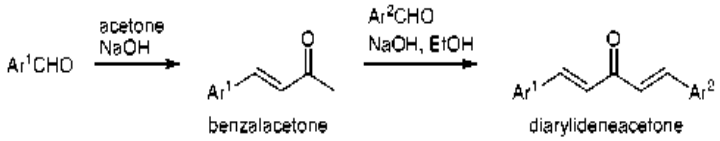
Keywords: heterocycles, catalysis, cross-coupling, isomerization, palladium, solvent effects, substituent effects

Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
Status : Postprint (Author's version)

The diarylideneacetone (DAA) core, namely 1,5-diaryl- penta-1,4-dien-3-one, is a widely represented structure, both in synthetic and naturally occurring compounds. In the field of advanced organic chemistry, dibenzylideneacetone has been found to be very useful, especially in organometallic catalysis; its uses as a ligand in the Suzuki- Miyaura coupling,[1] or in the Heck reaction,[2] is well documented. Diarylideneacetones can also be used as a starting material for the synthesis of highly substituted cyclopen- tenones through a Nazarov-type cyclization.[3] Their use in multicomponent reactions has been demonstrated, leading to the synthesis of highly functionalized vinylpyrazoline or indazole derivatives.[4] Besides these synthetic uses, DAAs have also been considered as promising lead compounds for the treatment of several diseases. Fairly close to the natural compound curcumin, known for numerous medicinal applications,[5] DAAs are currently being evaluated for their use in cancer therapy.[6] Their antioxidant activities have also turned out to be very promising,[7] as well as their effects on the regulation of the inflammatory pro- cess.[8] More recently, the use of diarylideneacetone derivatives as radiolabeled probes for P—amyloid plaque imaging has been proposed.[9]

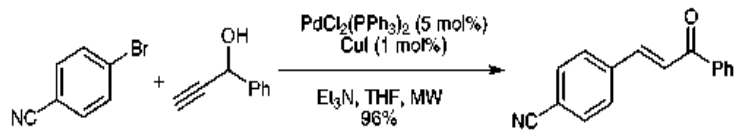
Diarylideneacetones are usually synthesized by a Claisen-Schmidt reaction (Scheme 1).[10] Although this straightforward procedure usually gives good yields, onlyreagents and products that withstand drastic concentrated basic or acidic reaction conditions can be used. Furthermore, heteroaromatic diarylideneacetones are very difficult to obtain through this aldol approach.[11] In particular, pyridyl-substituted penta-1,4-dien-3-ones have been synthesized via a much longer and complex HornerWadsworth-Emmons approach.12 Finally, besides these drawbacks, dissymmetric DAAs are not rapidly obtained via the Claisen-Schmidt protocol since the synthesis requires two condensation steps: first a benzalacetone is synthesized, and then allowed to react with a second benzaldehyde to give the desired dissymmetric DAA.[13] This procedure usually results in lower yields as various byproducts are formed.[14]

Scheme 1 *Claisen-Schmidt synthesis of diarylideneacetones (when $Ar^1 = Ar^2$, the reaction is performed in one pot)*



In order to circumvent these drawbacks and to develop a novel approach allowing the one-pot synthesis of dissymmetric (hetero)diarylideneacetones under mild conditions, we investigated a new, convenient catalytic pathway. Previously, we have reported a catalytic procedure for the synthesis of chalcones.[15] This methodology, called the coupling-isomerization reaction (CIR), is based on a Sonogashira coupling followed by an in situ isomerization, under basic conditions. Initially conducted under thermal conditions, the protocol was considerably improved by the use of microwave irradiation (Scheme 2).[16]

Scheme 2 *Synthesis of chalcones via a microwave-assisted coupling-isomerization reaction*



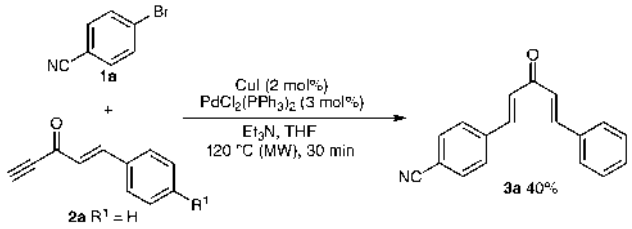
Considering the structural similarities between chalcones and diarylideneacetones, we aimed at adapting the CIR procedure to the synthesis of diarylideneacetones. Here, we report the first synthetic results and the optimization of the reaction of unsaturated propargyl alcohols with (het- ero)aryl halides, leading to

Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
Status : Postprint (Author's version)

(hetero)diarylideneacetones by palladium-catalyzed coupling and isomerization under microwave irradiation.

The initial attempts were made using 4-bromobenzonitrile (1a) and 1-phenylpent-1-en-4-yn-3-ol (2a) as starting materials. The catalytic system was composed of bis(triphe- nylphosphane)palladium(II) dichloride [PdCl2(PPh3)2] and copper iodide as a cocatalyst, without any additional ligand. The reaction was carried out in tetrahydrofuran at 120 °C (dielectric heating) for 30 minutes with triethylamine as the base of choice (Scheme 3). These conditions were selected further to previous studies on the synthesis of chalcones.15,16 The desired product 3a was obtained in 40% yield. From this encouraging result, we then optimized the reaction conditions. In order to make this process easier, we established an HPLC method for the quantitative determination of product 3a (Amax = 325 nm). With such a selective and accurate quantification method, we were able to study the effects of discrete factors (base, solvent, and catalyst) as well as continuous factors (irradiation time, temperature, and concentration).

Scheme 3 *First result on the synthesis of 3a via the couplingisomerization reaction*



Since the isomerization step of the CIR is a base-catalyzed process, the choice of the base is expected to be crucial. Six bases were selected according to their pKa values and their nucleophilic properties: cesium carbonate, triethylamine, piperidine, pyrrolidine, N,N-diisopropylethyl- amine (DIPEA), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Table 1). An inorganic base like cesium carbonate resulted in a limited amount of the desired product (Table 1, entry 1). Switching to organic bases, with the use of DBU, no product was detected (Table 1, entry 2). Although 4-bromobenzonitrile (1a) was still present in the mixture, neither the desired product nor the 1-phenylpent- 1-en-4-yn-3-ol (2a) was detected. DBU as a base might be too strong, inducing decomposition of the unsaturated propargyl alcohol, probably by the retro-Favorskii reaction. In the case of pyrrolidine, both starting materials were entirely consumed to form a new product, not the desired one, that we were not able to identify (Table 1, entry 3). With piperidine, no reaction occurred and the starting materials were still present (Table 1, entry 4). On the other

hand, with nonnucleophilic tertiary amines such as DIPEA and triethylamine, the reaction worked well (Table 1, entries 5 and 6). In the case of DIPEA, the coupling reaction occurred but the isomerization seemed to be slower, resulting in lower yield. The higher steric hindrance of DIPEA likely explains the lower reactivity compared to triethylamine. Consequently, triethylamine was selected as the base for this reaction.

Although the choice of solvent under conventional heating is very important, it becomes even more crucial for reactions under microwave irradiation.17 Taking into account these specificities, four different solvents were tested: tetrahydrofuran (THF), 1,4-dioxane, N,N-dimeth- ylformamide (DMF), and neat triethylamine. All four solvents resulted in satisfactory yields but THF was clearly less efficient than the others. 1,4-Dioxane, DMF, and neat triethylamine showed comparable results (Table 1, entries 7-9); however, as 1,4-dioxane resulted in the highest yield and is much easier to remove during workup, it was selected as the solvent for this reaction.

Table 1 *Optimization of the Discrete Factors in the Reaction of 1a with 2aa*

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Entry	Base	Solvent	Catalyst	Yield[b] of 3a (%)
1	Cs2CO3	THF	PdCl2(PPh3)2	5
2	DBU	THF	PdCl2(PPh3)2	0
3	pyrrolidine	THF	PdCl2(PPh3)2	0
4	piperidine	THF	PdCl2(PPh3)2	0
5	DIPEA	THF	PdCl2(PPh3)2	21
6	Et3N	THF	PdCl2(PPh3)2	40
7	Et3N	DMF	PdCl2(PPh3)2	58
8	Et3N	neat Et3N	PdCl2(PPh3)2	52
9	Et3N	1,4-dioxane	PdCl2(PPh3)2	62
10	Et3N	1,4-dioxane	Pd(PPh3)4	60

a Reactions at 0.3 M, with base (5 equiv), heated at 120 °C under microwave irradiation for 30 min.
b HPLC yields.

The first step in the CIR is a Sonogashira coupling which is usually performed using a palladium-phosphane ligand complex as a catalyst in the presence of a catalytic amount of a copper(I) salt, most often copper iodide. Regarding the palladium precatalyst, Pd(PPh3)4 or PdCl2(PPh3)2 are most commonly used in this type of reaction.18 We evaluated them both and the yields were 60% and 62%, respectively (Table 1, entries 9 and 10). In all cases, 20 mol% of triphenylphosphane was added to the reaction mixture to stabilize the palladium catalyst.16

For gathering a maximum of information with a minimum of experiments, we decided to apply the Design of Experiment (DoE) methodology. Here, a Box-Behnken design (BBD) was chosen.19 This design uses a centered quadratic model to calculate the three-dimensional representation (response surfaces) of multivariate systems, allowing the optimization of the process.20 Three factors required 15 experiments for the development of a BBD. Conditions for each run were chosen based on the specific matrix of experiments of the BBD (for the conditions and yields of the 15 experiments, see Supporting Information). Multivariate quadratic regression of the raw results allows the plotting of response surfaces, which helps to depict primary trends and to achieve a better understanding of the system (Figure 1).

Even at first glance, it was apparent that temperature has a drastic influence on the yield. A maximum was clearly reached around 120 °C; higher or lower temperatures resulted in a significant decrease in the yield (Figure 1, plots a and b). The molarity also plays an important role: higher seems to be better, but a plateau was reached between 0.5 and 0.6 mol·L-1 (Figure 1, plots a and c). Finally, the effect of irradiation hold time is less obvious as no tendency could be clearly detected (Figure 1, plots b and c). Nonlinear specific effects of microwave irradiation might explain this and make the hold-time term (and its combinations) statistically nonsignificant for the model.17 In order to confirm these primary trends, an algorithmic calculation was performed.21 Here, the maximal yield was predicted to reach 59% after 45 minutes of microwave irradiation at a temperature of 120 °C and at a concentration of 0.55 mol-L-1. To evaluate this expectation, we performed an experiment with starting materials 1a and 2a under the calculated optimal reaction conditions. The final yield after isolation and purification was 65%, confirming the computed prediction.

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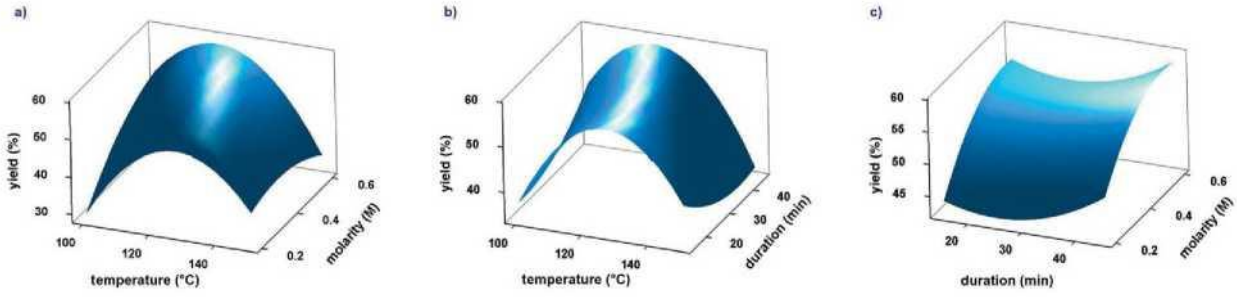
The methodology under these optimized conditions was then extended to the synthesis of several dissymmetric (hetero)dibenzylideneacetones 3 (Table 2). With respect to the aryl halide 1, the reaction proved to be fairly general for electron-deficient aryl halides (Table 2, entries 1, 2, and 9); however, under the standard conditions, electronrich aryl halides could not be successfully transformed into the title compounds (Table 2, entries 3-5). This behavior is in agreement with the prior general mechanistic insights gained on the CIR.15b Ongoing studies are directed toward developing optimal conditions for the implementation of the propargyl alcohols 2 into domino sequences where the sensitive diarylideneacetone functionality is in situ transformed to give more thermally stable cyclization products. On the other hand, heteroaryl halides, such as pyridyl, pyrimidinyl, and thiazolyl halides were transformed uneventfully, in good yields, to substituted heteroarylideneacetones otherwise difficult to access (Table 2, entries 6-8 and 10-12), even in the case of a fluorinated pyridine 1i as the substrate (Table 2, entry 11). On the propargylic alcohol substrate 2, both electro-neutral and electron-rich phenyl substituents are well tolerated (Table 2, entries 2, 7, 9, and 10). In addition, we also demonstrated that this procedure can be easily scaled up, as product 3a was successfully obtained on a 10-mmol scale in 68% yield using the same optimized conditions (Table 2, entry 1).

In conclusion, we have described a new synthetic methodology for the synthesis of dissymmetric (hetero)diaryli- deneacetones which overcomes many drawbacks of the classical Claisen-Schmidt reaction. Starting from an aryl halide and an unsaturated propargyl alcohol, this procedure allows the rapid one-pot synthesis of diarylideneace- tones under the mild conditions of a palladium-catalyzed coupling-isomerization reaction. The optimized reaction conditions were applied to several substrates, giving the desired products in moderate to good yield. The scope of the reaction was demonstrated, underlined by the synthesis of fluorinated, or heteroaromatic, dissymmetric di- arylideneacetones which cannot be obtained through the Claisen-Schmidt pathway.

Cinnamaldehydes, ethynylmagnesium bromide, aryl halides, palladium catalysts, copper iodide, amines, and triphenylphosphane were obtained from Sigma Aldrich and were used without further purification. Unsaturated propargyl alcohols were synthesized by ethynylation of the corresponding cinnamaldehyde. Unsaturated propargyl alcohol 2a was obtained following the published proce- dure,22 while product 2b was prepared as described below. THF, 1,4-dioxane, and DMF were dried by passage through an activated alumina column under argon and degassed by bubbling of argon for 15 min. Et3N and DIPEA were freshly distilled over KOH under argon and stored over KOH

Figure 1 *Plots of response surfaces. Hold values: a) duration = 45 min, b) molarity = 0.55 M, c) temperature = 120 °C.*



Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
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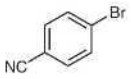
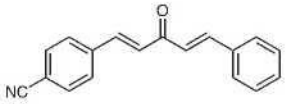
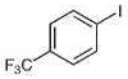
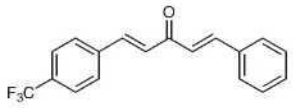
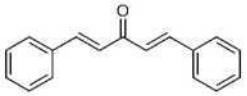
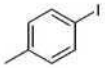
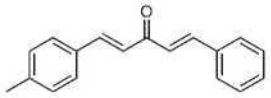
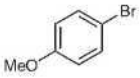
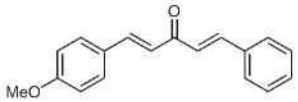
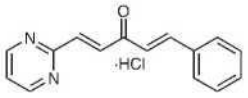
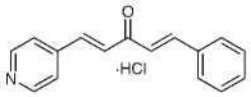
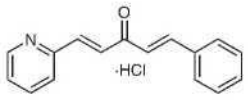
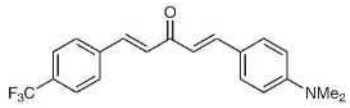
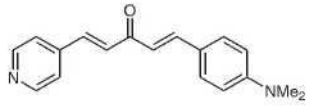
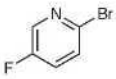
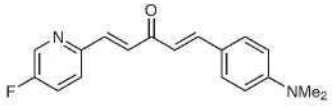
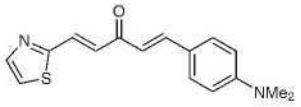
Table 2 *Scope of the Reactiona*

Entry	(Hetero)aryl halide **1**	Propargyl alcohol **2**	Diarylideneacetone **3**	Yield[b] (%)
1	**1a** 	**2a** $R^1 = H$	**3a** 	65 68[c]
2	**1b** 	**2a**	**3b** 	55
3	**1c** 	**2a**	**3c** 	<5
4	**1d** 	**2a**	**3d** 	0
5	**1e** 	**2a**	**3e** 	0
6	**1f** 	**2a**	**3f** 	65
7	**1g** 	**2a**	**3g** 	42
8	**1h** 	**2a**	**3h** 	50
9	**1b**	**2b** $R^1 = NMe_2$	**3i** 	58
10	**1g**	**2b**	**3j** 	54
11	**1i** 	**2b**	**3k** 	52
12	**1j** 	**2b**	**3l** 	62

a Reactions on a 1-mmol scale, using the optimized conditions.
b Isolated yields.
c Scale-up; reaction performed on a 10-mmol scale

Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
Status : Postprint (Author's version)

All reactions were performed in standard microwave glassware, which was dried, flushed with argon, and sealed. Two chemistry- dedicated microwave reactors (Biotage and CEM) were used with comparable results. Temperature and pressure were automatically controlled by the apparatus. Flash chromatography was performed on silica gel 60 (230-400 mesh, 40-63 µm) purchased from E. Merck. Thin-layer chromatography was performed on aluminum sheets coated with silica gel 60 F254 purchased from E. Merck. UV-vis spectra were recorded on a Varian Cary 50 spectrophotometer. HPLC experiments were performed on a Hewlett Packard HPLC with dual UV-vis detection (254 and 325 nm). Samples (0.8 pL) were eluted on a Nucleosil silica column with CH2Cl2 containing 1 vol% of i-PrOH for 30 min at 0.60 mL·min-1. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded on Bruker AC 200, 300, 400, or 500 MHz instruments with solvent peaks as reference. Carbon multiplicities were assigned by Distortionless Enhancement by Polarization Transfer (DEPT) and Heteronuclear Single Quantum Correlation (HSQC) experiments. The 1H signals were assigned by 2D experiments (COSY). ESI-HRMS data were recorded on a Bruker mi- crOTOF spectrometer. Melting points were measured on a Stuart Melting Point 10 apparatus and are given uncorrected.

(E)-1-[4-(Dimethylamino)phenyl]pent-1-en-4-yn-3-ol (2b)

In a dry three-necked round-bottomed flask were introduced anhyd THF (5 mL) and 1 M ethynylmagnesium bromide in THF (18 mL). The solution was cooled at -78 °C and (E)-3-[4-(dimethylami- no)phenyl]acrylaldehyde (1.23 g, 7 mmol) in anhyd THF (7 mL) was added dropwise over 10 min at -78 °C under stirring and argon. The mixture was next allowed to warm to r.t. and the reaction was carried out for 2 h under stirring and argon. The reaction was subsequently quenched with sat. aq NH4Cl (20 mL). The product was extracted with Et2O (3 x 30 mL) after the aqueous layer was adjusted to pH ~10 with NaHCO3. The combined organic layers were dried (MgSO4), filtered, and evaporated to dryness. The orange crude powder was recrystallized (hexanes-toluene, 4:6) to give 2b as a pure brown powder; yield: 1.10 g (79%).

Mp 123-125 °C.

^{1}H NMR (300 MHz, acetone-d6): δ= 7.30 (d, ^{3}J = 8.7 Hz, 2 H, ArH), 6.71 (d, ^{3}J = 8.7 Hz, 2 H, ArH), 6.63 (d, ^{3}J = 15.8 Hz, 1 H, vinylic), 6.10 (dd, ^{3}J = 15.8, 6.3 Hz, 1 H, vinylic), 4.97 [ddd, ^{3}J =6.3, 5.9 Hz, ^{4}J = 2.0 Hz, 1 H, CH(OH)], 4.53 (d, ^{3}J = 5.9 Hz, 1 H, OH), 2.98 (d, ^{4}J = 2.0 Hz, 1 H, alkyne), 2.95 [s, 6 H, N(CH3)2].

^{13}C NMR (50.3 MHz, acetone-d6): 8 = 151.5, 131.8, 128.5, 125.6, 125.4, 113.2, 85.5, 74.4, 63.1, 40.5.

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.37; H, 7.52; N, 6.94.

1,5-Diarylpenta-1,4-dien-3-ones 3; General Procedure

An aryl halide 1 (1 mmol, 1 equiv), an unsaturated propargyl alcohol 2 (1.2 mmol, 1.2 equiv), PdCl2(PPh3)2 (21 mg, 0.03 mmol, 3 mol%), CuI (4 mg, 0.02 mmol, 2 mol%), and Ph3P (52 mg, 0.2 mmol, 20 mol%) were introduced in a 10-mL microwave vial flushed with argon. The mixture was solubilized with a soln of an- hyd Et3N (700 pL, 5 mmol, 5 equiv) in anhyd degassed 1,4-dioxane (1.3 mL). The solution was heated under microwave irradiation at 120 °C for 45 min. The reaction mixture was poured into a mix of 1 M aq HCl (10 mL) and sat. aq NH4Cl (10 mL), and this was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried (MgSO4), filtered, and evaporated to dryness to give crude product which was purified by flash chromatography.

Where indicated, the free base was dissolved in Et2O (5 mL) and 1.25 M HCl in EtOH (2 mL) was added. The suspension was filtered to recover the hydrochloride salt of the desired compound.

4-[(1E,4E)-3-Oxo-5-phenylpenta-1,4-dien-1-yl]benzonitrile (3a) Pure, light yellow powder; yield: 169 mg (65%).

Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
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Scale-up on 10 mmol; yield: 1.75 g (68%).

Mp 146 °C.

IR (neat): 1674, 1601, 1337, 1188, 982, 826, 763, 695 cm-1.

^{1}H NMR (500 MHz, CD2C12): δ = 7.75 (d, ^{3}J = 16.4 Hz, 1 H, vinylic), 7.72 (m, 4 H, ArH), 7.69 (d, ^{3}J= 15.5 Hz, 1 H, vinylic), 7.667.64 (m, 2 H, ArH), 7.44 (m, 3 H, ArH), 7.18 (d, ^{3}J= 15.5 Hz, 1 H, vinylic), 7.09 (d, ^{3}J = 16.4 Hz, 1 H, vinylic).

^{13}C NMR (125 MHz, CD2C12): δ = 188.3, 144.1, 140.7, 139.6, 135.0, 133.0, 131.1, 129.4, 129.0, 128.8, 128.5, 125.7, 118.8, 113.7.

HRMS (ESI+): m/z [M+Na]+ calcd for $C_{18}H_{13}NO$: 282.089; found: 282.089.

(1E,4E)-1-Phenyl-5-[4-(trifluoromethyl)phenyl]penta-1,4-dien- 3-one (3b)

Pure, pale yellow powder; yield: 166 mg (55%).

Mp 142-143 °C.

IR (neat): 1653, 1593, 1322, 1107, 1066, 981, 826, 760, 695 cm-1.

^{1}H NMR (300 MHz, CDC13): δ = 7.79 (d, ^{3}J = 16.0 Hz, 1 H, vinylic), 7.76 (d, ^{3}J= 16.0 Hz, 1 H, vinylic), 7.77-7.67 (m, 4 H, Ar), 7.67-7.60 (m, 2 H, Ph), 7.45 (m, 3 H, Ph), 7.17 (d, ^{3}J= 16.0 Hz, 1 H, vinylic), 7.10 (d, ^{3}J= 16.0 Hz, 1 H, vinylic).

^{13}C NMR (75.5 MHz, CDC13): δ = 188.7, 144.2, 141.4, 138.4 (m, Cq), 134.8, 132.1 (q, 2JC-F = 32 Hz, Cq), 131.0, 129.2, 128.7, 128.6, 127.6, 125.9 (q, ^{3}JC-F = 3.6 Hz, CH), 125.5, 123.8 (q, 1JC-F = 271 Hz, Cq).

HRMS (ESI+): m/z [M+Na]+ calcd for $C_{18}H_{13}F_3O$: 325.081; found: 325.081.

(1E,4E)-1-Phenyl-5-(pyrimidin-2-yl)penta-1,4-dien-3-one Hydrochloride (3f)

Pure, fine yellow powder; yield: 178 mg (65%).

Mp 164 °C (dec).

IR (neat): 1662, 1604, 1595, 1504, 1386, 1238, 1200, 1061, 994, 986, 813, 780, 692 cm-1.

^{1}H NMR (300 MHz, DMSO-d6): δ = 8.92 (d, ^{3}J = 4.9 Hz, 2 H, H- 4/6 pyrimidine), 7.83 (m, 2 H, Ph), 7.78 (d, ^{3}J= 16.0 Hz, 1 H, vinylic), 7.77 (d, ^{3}J= 15.8 Hz, 1 H, vinylic), 7.64 (d, ^{3}J= 15.8 Hz, 1 H, vinylic), 7.52 (d, ^{3}J = 4.6 Hz, 1 H, H-5 pyrimidine), 7.47 (d, ^{3}J = 16.0 Hz, 1 H, vinylic), 7.46 (m, 3 H, Ph).

^{13}C NMR (75.5 MHz, DMSO-d6): δ = 188.7, 162.3, 157.7, 143.9, 140.6, 134.4, 133.3, 130.8, 128.9, 128.8, 125.2, 121.0.

HRMS (ESI+): m/z [M + Na]+ calcd for $C_{15}H_{12}N_2O$: 259.084; found: 259.084.

(1E,4E)-1-Phenyl-5-(pyridin-4-yl)penta-1,4-dien-3-one Hydrochloride (3g)

Pure, fine yellow powder; yield: 115 mg (42%).

Mp 190 °C (dec).

IR (neat): 1655, 1634, 1602, 1505, 1335, 1189, 979, 812, 767, 729, 691 cm-1.

^{1}H NMR (300 MHz, DMSO-d6): δ = 8.97 (d, ^{3}J = 6.4 Hz, 2 H, H- 2/6 pyridine), 8.38 (d, ^{3}J = 6.4 Hz, 2 H, H-3/5 pyridine), 8.05-7.85 (m, 3 H, vinylic), 7.82 (m, 2 H, Ph), 7.49 (m, 3 H, Ph), 7.33 (d, ^{3}J = 16.8 Hz, 1 H, vinylic).

^{13}C NMR (75.5 MHz, DMSO-d6): δ = 188.4, 150.2, 144.8, 143.0, 137.0, 134.4, 133.4, 131.0, 129.1, 128.7, 125.7, 125.1.

HRMS (ESI+): m/z [M+H]+ calcd for $C_{16}H_{13}NO$: 236.107; found: 236.106.

Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
Status : Postprint (Author's version)

(1E,4E)-1-Phenyl-5-(pyridin-2-yl)penta-1,4-dien-3-one Hydrochloride (3h)

Pure, fine yellow powder; yield: 136 mg (50%).

Mp 155 °C (dec).

IR (neat): 1661, 1614, 1462, 1304, 1197, 1109, 979, 771, 692 cm-1.

^{1}H NMR (300 MHz, DMSO-d6): δ = 8.83 (d, ^{3}J = 5.6 Hz, 1 H, H-6 pyridine), 8.38-8.26 (m, 2 H, pyridine), 8.09 (d, ^{3}J=16.4Hz,1H, vinylic), 7.99 (d, ^{3}J= 15.9 Hz, 1 H, vinylic), 7.84 (d, ^{3}J= 16.4 Hz, 1 H, vinylic), 7.84-7.81 (m, 1 H, pyridine), 7.81 (m, 2 H, Ph), 7.47 (m, 3 H, Ph), 7.29 (d, ^{3}J= 15.9 Hz, 1 H, vinylic).

^{13}C NMR (75.5 MHz, DMSO-d6): δ = 188.2 (Cq), 149.5 (Cq pyridine), 145.5 (CH), 144.7 (CH), 142.6 (CH), 135.7 (Cq), 134.4 (CH), 131.5 (CH), 130.9 (CH), 129.1 (CH phenyl), 128.8 (CH phenyl), 126.3 (CH), 126.0 (CH), 125.9 (CH).

HRMS (ESI+): m/z [M+Na]+ calcd for $C_{16}H_{13}NO$: 258.089; found: 258.088.

(1E,4E)-1-[4-(Dimethylamino)phenyl]-5-[4-(trifluorometh- yl)phenyl]penta-1,4-dien-3-one (3i)

Pure, bright orange powder; yield: 200 mg (58%).

Mp 179-180 °C.

IR (neat): 1648, 1600, 1587, 1524, 1321, 1162, 1118, 1108, 1065, 981, 826, 810 cm-1.

1H NMR (500 MHz, $CDCl_3$): δ =7.76 (d, ^{3}J= 15.6 Hz, 1 H, vinylic), 7.72 (d, ^{3}J= 16 Hz, 1 H, vinylic), 7.70 (m, 4 H, ArH), 7.55 (d,

^{3}J=9Hz, 2 H, ArH), 7.17 (d, ^{3}J= 16 Hz, 1 H, vinylic), 6.89 (d, ^{3}J= 15.6 Hz, 1 H, vinylic), 6.72 (d, ^{3}J=8.5 Hz, 2 H, ArH), 3.07 [s, 6 H, N(CH3)2].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 188.5, 152.4, 145.2, 140.1, 138.9 (m, Cq), 131.4 (q, 2JC-F = 32.5 Hz, Cq), 130.7, 128.5, 128.1, 126.0 (q, ^{3}JC-F = 3.8 Hz, Ar), 123.9 (q, 1JC-F = 269 Hz, Cq), 122.5, 120.8, 112.1, 40.3.

HRMS (ESI+): m/z [M+H]+ calcd for $C_{20}H_{18}F_3NO$: 346.141; found: 346.140.

(1E,4E)-1-[4-(Dimethylamino)phenyl]-5-(pyridin-4-yl)penta- 1,4-dien-3-one (^{3}J)

Pure orange powder; yield: 150 mg (54%).

Mp 192 °C (dec).

IR (neat): 1662, 1634, 1609, 1509, 1197, 1131, 1114, 992, 836, 819 cm-1.

1H NMR (300 MHz, $CDCl_3$): δ =8.68 (d, ^{3}J= 6.0 Hz, 2 H, H-2/6 pyridine), 7.76 (d, ^{3}J= 15.6 Hz, 1 H, vinylic), 7.61 (d, ^{3}J= 15.9 Hz, 1 H, vinylic), 7.54 (d, ^{3}J=8.5Hz, 2 H, ArH), 7.46 (d, ^{3}J=6.0Hz, 2 H, H-3/5 pyridine), 7.25 (d, ^{3}J= 15.9 Hz, 1 H, vinylic), 6.87 (d, ^{3}J= 15.6 Hz, 1 H, vinylic), 6.71 (d, ^{3}J=8.5 Hz, 2 H, ArH), 3.07 [s, 6 H, N(CH3)2].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 186.0, 152.3, 150.5, 145.4, 142.5, 138.7, 130.6, 129.6, 122.1, 122.0, 120.4, 111.9, 40.1.

HRMS (ESI+): m/z [M+H]+ calcd for C18H18N2O: 279.149; found: 279.149.

(1E,4E)-1-[4-(Dimethylamino)phenyl]-5-(5-fluoropyridin-2- yl)penta-1,4-dien-3-one (3k)

Pure orange powder; yield: 154 mg (52%).

Mp 164 °C (dec).

IR (neat): 1605, 1559, 1523, 1475, 1434, 1371, 1345, 1226, 1186, 1098, 982, 855, 803 cm-1.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, ^{3}JH-F = 2.7 Hz, 1 H, H-6 pyridine), 7.77 (d, ^{3}J= 15.9 Hz, 1 H, vinylic), 7.68 (d,

Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
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^{3}J= 15.6 Hz, ^{1} H, vinylic), 7.57 (d, ^{3}J= 15.6 Hz, 1 H, vinylic), 7.54 (d, ^{3}J= 8.6 Hz, 2 H, ArH), 7.5-7.4 (m, 2 H, pyridine), 6.89 (d, ^{3}J= 15.9 Hz, 1 H, vinylic), 6.72 (d, ^{3}J=8.6Hz, 2 H, ArH), 3.07 [s, 6 H, N(CH3)2].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 188.8, 159.4 (d, 1JC-F = 260 Hz), 152.1, 150.1 (d, ^{4}JC-F=4Hz), 145.0, 138.8, 138.7 (d, 2JC-F = 24 Hz), 130.5, 128.8, 125.8 (d, ^{3}JC-F = 5 Hz), 123.3 (d, 2JC-F = 19 Hz), 122.5, 121.4, 112.0, 40.2.

HRMS (ESI+): m/z [M +H]+ calcd for $C_{18}H_{17}FN_2O$: 297.140; found: 297.139.

(1E,4E)-1-[4-(Dimethylamino)phenyl]-5-(1,3-thiazol-2-yl)pen- ta-1,4-dien-3-one (3l)

Pure, dark purple powder; yield: 176 mg (62%).

Mp 176 °C.

IR (neat): 1594, 1558, 1524, 1346, 1186, 1099, 1074, 1000, 811, 771 cm-1.

>H NMR (300 MHz, CDC13): δ = 7.96 (d,^{3}J =3.2 Hz, 1 H, H-4 thiazole), 7.80 (d, ^{3}J= 15.8 Hz, 1 H, vinylic), 7.76 (d, ^{3}J= 15.8 Hz, ^{1} H, vinylic), 7.53 (d, ^{3}J= 8.7 Hz, 2 H, ArH), 7.46 (d, ^{3}J =3.2Hz, 1 H, H-5 thiazole), 7.43 (d, ^{3}J= 15.8 Hz, 1 H, vinylic), 6.88 (d, ^{3}J= 15.8 Hz, 1 H, vinylic), 6.73 (d, ^{3}J= 8.7 Hz, 2 H, ArH), 3.07 [s, 6 H, $N(CH_3)2$].

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 187.9, 164.6, 152.1, 145.3, 144.7, 132.5, 130.6, 129.5, 122.5, 121.2, 120.7, 112.0, 40.2.

HRMS (ESI+): m/z [M+H]+ calcd for $C_{16}H_{16}N_2OS$: 285.106; found: 285.105.

Acknowledgment

This work was supported by the Fonds der Chemischen Industrie, the Deutscher Akademischer Austauschdienst (DAAD, scholarship for T.G.), the collaborative center SFB 544 (B14 project), the Centre National de la Recherche Scientifique (CNRS), the University of Strasbourg (UMR 7509 CNRS-UdS), the ANRémergence program (grant SCHISMAL to E.D.C.), and the International Center for Frontier Research in Chemistry in Strasbourg (www.icfrc.fr). T.G. is grateful to the MENRT (French Ministry of Research) for his PhD salary. We would like to thank Prof. D. Wolbert for his valuable advice on the DoE methodology.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.SIfrupignoomrtioatnSIfrupgnoomprtioan

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Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
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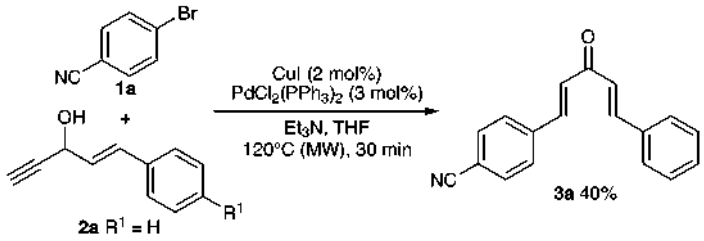
Published in : Journal (année), vol. xx, n°xx, pp. xx–xx
DOI:xxxxxxxxxxxxxxx
Status : Postprint (Author's version)

ERRATUM: VERSATILE SYNTHESIS OF DISSYMMETRIC DIARYLIDENEACETONES VIA A PALLADIUM-CATALYZED COUPLING-ISOMERIZATION REACTION

Thibault Gendron, Elisabeth Davioud-Charvet, Thomas J. J. Müller* Synthesis 2012, 44, 3829.

In Scheme 3, page 3830, the authors have noticed a mistake, which unfortunately has been overlooked upon checking the galley proofs. Compound 2a is falsely drawn as a propargyl ketone instead of being a propargyl alcohol, as it should be. The correct scheme is shown below.



Scheme 3