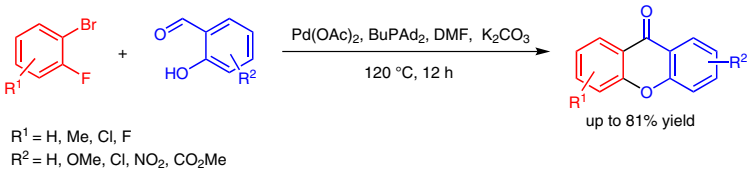
Synlett C. Shen, X.-F. Wu Letter

Selective Preparation of Xanthones from 2-Bromofluorobenzenes and Salicylaldehydes via Palladium-Catalyzed Acylation–S_NAr Approach

Chaoren Shen
Xiao-Feng Wu*

Leibniz-Institut für Katalyse an der Universität Rostock e.V.,
Albert-Einstein-Str. 29a, 18059 Rostock, Germany
xiao-feng.wu@catalysis.de



R^1 = H, Me, Cl, F
R^2 = H, OMe, Cl, NO_2, CO_2Me

Received: 25.11.2015
Accepted: 12.01.2016
Published online: 04.02.2016
DOI: 10.1055/s-0035-1561563; Art ID: st-2015-b0915-l

Abstract A regioselective pathway for the preparation of xanthones from 2-bromofluorobenzenes and salicylaldehydes has been developed. The reaction proceeded through palladium-catalyzed acylation–S_NAr sequence. Good to moderate yields of the desired xanthones were prepared in one step. Based on the results of control experiments, a possible reaction mechanism has been proposed.

Key words xanthone, palladium catalyst, coupling, heterocycle synthesis, acylation, nucleophilic substitution

As the central core of a variety of naturally occurring organic compounds and secondary metabolites produced by many bacteria,[1] xanthone is one of the 'privileged' heterocycle skeletons in organic chemistry.[2] Thus, the construction of xanthone scaffold has always been synthetically attractive due to the practical application[3] and diverse biological activities[4] of xanthones and their derivatives.[5] Traditionally, Friedel–Crafts acylation is the classical approach to construct xanthones via benzophenone intermediates.[6] However Friedel–Crafts acylation not only suffers from low regioselectivity and poor functional-group tolerance but also requires overstoichiometric Lewis acid. Recently, various new methodologies have been developed for the preparation of xanthones.[7] Palladium-catalyzed acylation of aryl halides with aldehydes is one of the procedures for building the benzophenone unit.[7l,8] To the best of our knowledge, only one example of utilizing palladium-catalyzed acylation to synthesize xanthones has been reported[7l] by employing 1,2-dibromoarenes as starting material which leads to the issue on regionselectivity and limited substrate scope. Therefore we intended to develop a palladium-catalyzed acylation–S_NAr approach with commercially available substrates and to achieve the regioselective synthesis of xanthones.

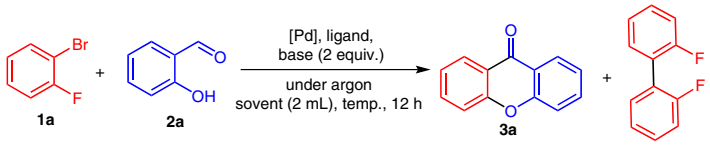
Using 2-bromofluorobenzene (**1a**) and salicylaldehyde (**2a**) as the standard substrates, conditions were investigated (Table 1). Initially, we found that 41% yield of the desired product was obtained with 2.5 mol% $PdCl_2(PPh_3)_2$ as the precatalyst and 2.0 equivalents K_2CO_3 as the base in DMF at 120 °C (Table 1, entry 1). Besides the xanthone product, 25% of 2,2′-difluoro-1,1′-biphenyl as the major side product were isolated as well. The biaryl byproduct was generated from the palladium-catalyzed homocoupling of **1a**. The generation of homocoupling byproduct also leads to the incomplete conversion of salicylaldehyde. Besides the side reaction, the premature decomposition of palladium catalyst and formation of palladium black in the solution of reductive salicylaldehyde contributed to the low yield. Therefore various measures including changing solvents (Table 1, entries 2–4) and bases (Table 1, entries 5 and 6), employing $Pd(PPh_3)_4$ (Table 1, entry 7) and adjusting reaction temperature (Table 1, entries 8 and 9) were attempted to inhibit the side reaction and palladium black precipitation. Nevertheless none of them can further improve the yield and inhibit the side reaction or generation of palladium black. The elevated temperature accelerated the deposition of palladium black. Increasing the palladium loading also has no significant promotion on the yield (Table 1, entry 10). To exclude the potential catalytic activity of deposed palladium black, palladium on activated charcoal was also examined (Table 1, entry 11). It proves that palladium black has no catalytic activity. Trials of $Pd(OAc)_2$ with BINAP and DPPF ligands show that bidentate phosphine ligand is not suitable for this reaction (Table 1, entries 12 and 13). Although electron-rich tributylphosphine ligand is able to effectively inhibit the generation of palladium black, it prohibits the reaction as well (Table 1, entries 14 and 15). Tris(4-methoxyphenyl)phosphine, more electron-rich analogue of

triphenylphosphine, cannot manage to improve the yield (Table 1, entry 16). To our delight, when bulky electron-rich trialkylphosphine ligand *n*-BuPAd$_2$ was employed, no palladium black precipitated (Table 1, entry 17). Further increasing the palladium and ligand loading can boost the yield, though the homocoupling side product of **1a** and unconverted salicylaldehyde still can be detected by GC–MS.

Having established the optimized reaction conditions, we investigated the substrate scope of this reaction (Scheme 1).[9] We found that the optimized reaction conditions are also applicable with 2-iodofluorobenzene as substrate (**3a**). For substituted salicylaldehydes with an electron-neutral or electron-donating group, good to moderate yields can be achieved with the protocol (**3b**–**d**). The reaction conditions displayed tolerance to the chlorine substituent on salicylaldehyde (**3e** and **3f**). However, for salicylaldehydes with a strong electron-withdrawing group, such as nitro and methoxycarbonyl, on the *para* position of hydroxyl group, no desired xanthone product **3g** or **3h** was obtained. For various substituted *o*-bromofluorobenzenes except 1-bromo-2,4-difluorobenzene (**1k**) and 1-bromo-4-chloro-2-fluorobenzene (**1l**), the desired substituted xanthone products can be obtained in moderated yields. For **1k** and **1l**, besides homocoupling byproduct biaryls and trace target products, several kinds of unidentified side products were observed on GC–MS. Moreover moderate yields were achieved with the protocol on the reaction between substituted *o*-bromofluorobenzenes and salicylaldehydes in general.

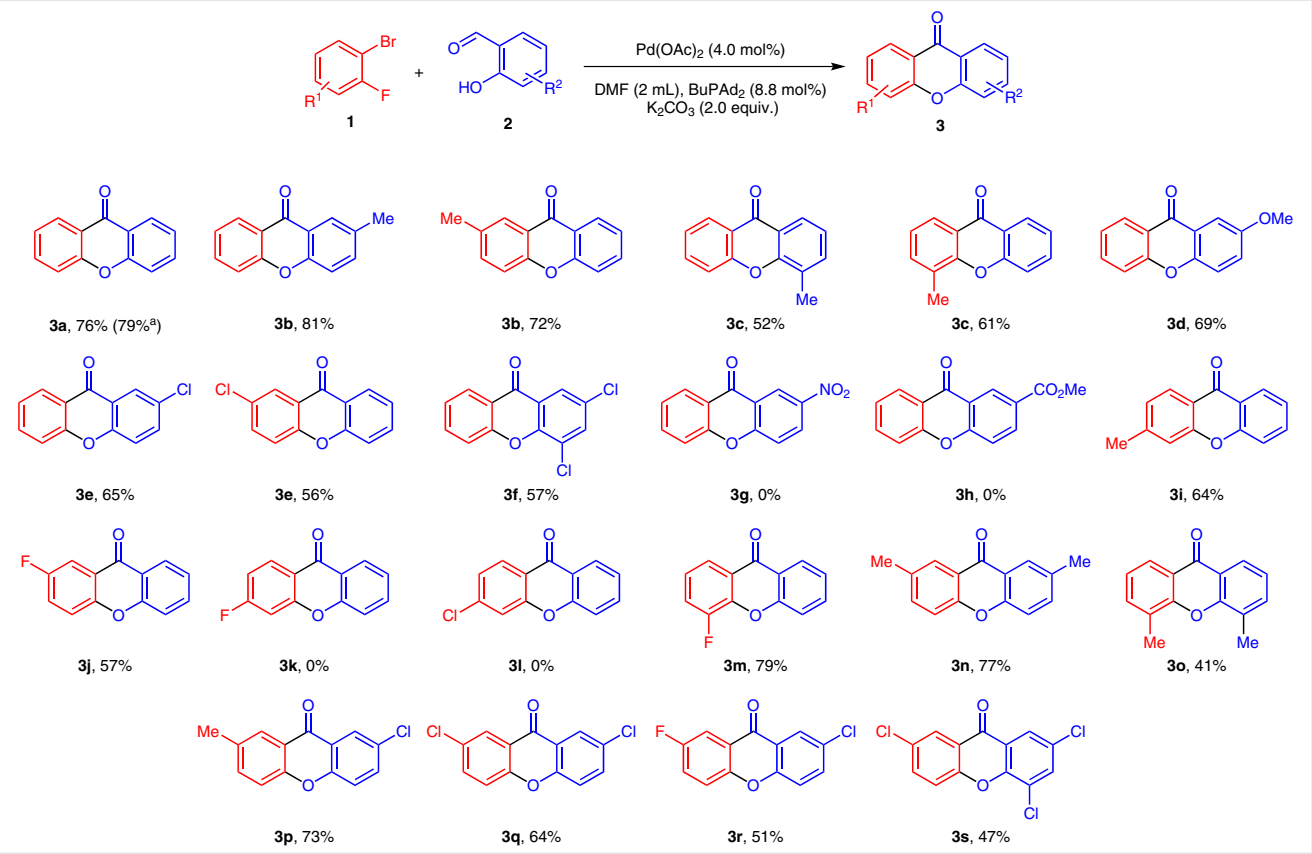
In order to have an insight into the reaction mechanism, a set of control reactions were conducted (Scheme 2). Firstly, it was found that both phenyl bromide and iodobenzene can react smoothly with salicylaldehyde under the standard reaction conditions to generate the corresponding 2-hydroxybenzophenone while homocoupling side product biphenyl was detected on GC–MS as well (Scheme 2, a). When *o*-bromofluorobenzene reacted with phenol instead of salicylaldehyde, the conversion of *o*-bromofluorobenzene was less than 5%. No 1-fluoro-2-phenoxybenzene or 1-bromo-2-phenoxybenzene but trace amount of 2,2′-difluoro-1,1′-bi-

Table 1 Optimization of Conditions[a]



Entry	[Pd] (mol%)	Ligand (mol%)	Base	Solvent	Temp (°C)	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$ (2.5)	–	K_2CO_3	DMF	120	41
2	$PdCl_2(PPh_3)_2$ (2.5)	–	K_2CO_3	1,4-dioxane	120	0
3	$PdCl_2(PPh_3)_2$ (2.5)	–	K_2CO_3	toluene	120	0
4	$PdCl_2(PPh_3)_2$ (2.5)	–	K_2CO_3	DMAc	120	21
5	$PdCl_2(PPh_3)_2$ (2.5)	–	Na_2CO_3	DMF	120	0
6	$PdCl_2(PPh_3)_2$ (2.5)	–	Cs_2CO_3	DMF	120	0
7	$Pd(PPh_3)_4$ (2.5)	–	K_2CO_3	DMF	120	38
8	$PdCl_2(PPh_3)_2$ (2.5)	–	K_2CO_3	DMF	130	21
9	$PdCl_2(PPh_3)_2$ (2.5)	–	K_2CO_3	DMF	105	35
10	$PdCl_2(PPh_3)_2$ (5.0)	–	K_2CO_3	DMF	120	51
11	Pd/C (5 wt%) (2.5)	–	K_2CO_3	DMF	120	0
12	$Pd(OAc)_2$ (2.5)	*rac*-BINAP (3.0)	K_2CO_3	DMF	120	0
13	$Pd(OAc)_2$ (2.5)	DPPF (3.0)	K_2CO_3	DMF	120	0
14	$Pd(OAc)_2$ (2.5)	*t*-$Bu_3P{\cdot}HBF_4$ (5.5)	K_2CO_3	DMF	120	13
15	$Pd(OAc)_2$ (2.5)	*n*-$Bu_3P{\cdot}HBF_4$ (5.5)	K_2CO_3	DMF	120	0
16	$Pd(OAc)_2$ (2.5)	$(p\text{-}MeOC_6H_4)_3P$ (5.5)	K_2CO_3	DMF	120	42
17	$Pd(OAc)_2$ (2.5)	*n*-BuPAd$_2$ (5.5)	K_2CO_3	DMF	120	43
18	$Pd(OAc)_2$ (4.0)	*n*-BuPAd$_2$ (8.8)	K_2CO_3	DMF	120	76

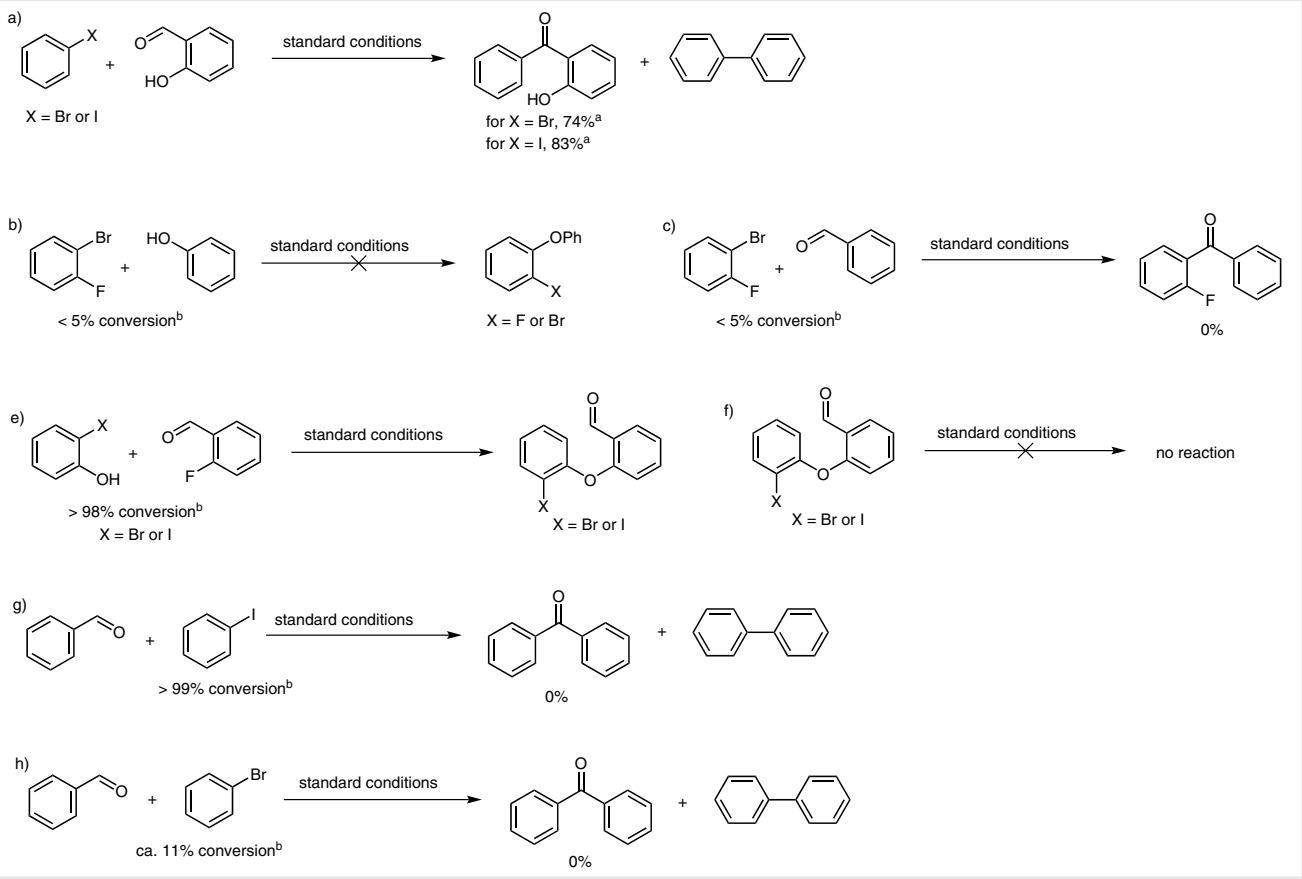
[a] Ad = 1-adamantyl; *rac*-BINAP = (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; DPPF = 1,1′-bis(diphenylphosphino)ferrocene; DMF = *N*,*N*-dimethylformamide; DMAc = *N*,*N*-dimethylacetamide.
[b] Isolated yields.



Scheme 1 Substrate scope of the reaction. Unless otherwise stated, reaction conditions: **1** (0.50 mmol), **2** (0.50 mmol), K_2CO_3 (2.0 equiv.), 4 mol% $Pd(OAc)_2$, 8.8 mol% *n*-$BuPAd_2$, DMF (2 mL), Ar, 120 °C, 12 h. Isolated yields are given. [a] 1-Fluoro-2-iodobenzene instead of 1-bromo-2-fluorobenzene.

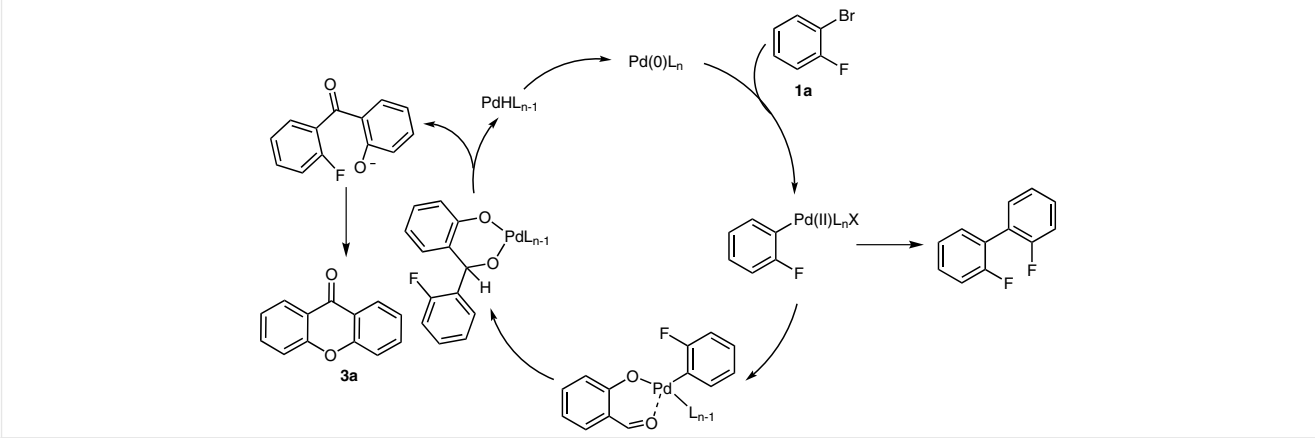
phenyl was observed on GC–MS (Scheme 2, b). It indicates that palladium-catalyzed acylation is prior to S_NAr. No 2-fluorobenzophenone but still trace amount of 2,2′-difluoro-1,1′-biphenyl was observed in the reaction of *o*-bromofluorobenzene with benzaldehyde on GC–MS (Scheme 2, c). When we attempted to exchange the sequence of acylation and S_NAr, although both 2-halogen phenol and 2-fluorobenzaldehyde are consumed, only the molecular ion peak of S_NAr product can be observed on GC–MS (for X = Br, *m/z* = 276 and 278, for X = I, *m/z* = 324) and no desired xanthone or even homocoupling byproduct was detected (Scheme 2, e). Intramolecular acylation can proceed with neither 2-(2-iodophenoxy)benzaldehyde nor 2-(2-bromophenoxy)benzaldehyde (Scheme 2, f). These suggest that ether cannot replace the role of hydroxyl group in the palladium-catalyzed acylation. Further investigation on the reaction of iodobenzene with benzaldehyde revealed that although neither conversion of benzaldehyde nor generation of benzophenone was observed on GC, iodobenzene was consumed and biphenyl was formed from the homocoupling of phenyl iodide[10] (Scheme 2, g). Similar result was also obtained in the reaction between bromobenzene and benzaldehyde, but the conversion of bromobenzene is much lower (Scheme 2, h). The above results of control reactions imply that the hydroxyl group plays an important role in palladium-catalyzed acylation of aryl bromide or aryl iodide with salicylaldehyde.

Based on the results of control experiments and the properties of acyl–palladium(II) complex,[11] we proposed a plausible reaction mechanism that is different from the previous reported plausible reaction mechanism involving acyl–palladium(II) and acyl–palladium(IV) complexes.[7l,8b] Our proposed plausible mechanism is a Heck-like process (Scheme 3).[8c,e] Compound **1a** first undergoes oxidative addition of palladium(0) complex to generate the aryl–palladium(II) intermediate. Then the aryl–palladium(II) intermediate coordinates with salicylaldehyde anion to form complex **A** in the basic solution and followed by the formation of complex **B** through the addition of aryl–palladium(II) onto the C=O double bond. After β-hydrogen elimination and following intramolecular S_NAr, xanthone is generated. When transmetalation between aryl–palladium(II) intermediates takes place and reductive elimination follows, the biaryl side product forms.[12]



Scheme 2 Control reactions. Unless otherwise stated, standard reaction conditions: aryl bromide or aryl iodide (0.50 mmol), salicylaldehyde or benzaldehyde or phenol (0.50 mmol), K_2CO_3 (2.0 equiv.), $Pd(OAc)_2$ (4 mol%), *n*-BuPAd$_2$ (8.8 mol%), DMF (2 mL), Ar, 120 °C, 12 h. [a] Isolated yield. [b] Conversion determined with *n*-hexadecane as internal standard.

In conclusion, we have achieved the selective preparation of xanthone from commercially available 2-bromofluorobenzenes and salicylaldehydes utilizing palladium-catalyzed acylation–S_NAr approach. Moderate to good yields with excellent regioselectivity can be achieved. Based on our control reactions, a plausible mechanism with a Heck-like process has been proposed.



Scheme 3 A plausible mechanism

Acknowledgment

The authors thank the state of Mecklenburg-Vorpommern, the Bundesministerium für Bildung und Forschung (BMBF), and the Deutsche Forschungsgemeinschaft for financial support. Thanks also go to China Scholarship Council (CSC) for their financial support to C. Shen (No. 201406230040). We also thank Dr. C. Fischer, S. Schareina, A. Koch, and S. Buchholz for their excellent technical and analytical support. We also appreciate the general support from Prof. Matthias Beller.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561563.

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(9) **General Procedure for the Synthesis of Xanthone**
To an oven-dried 25 mL Schlenk tube containing a stirring bar was added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), *n*-$BuPAd_2$ (15.7 mg, 0.44 mmol), 2-bromofluorobenzene (0.50 mmol), salicylaldehyde (0.50 mmol), K_2CO_3 (1.0 mmol). The Schlenk tube was vacuumed and then purged with argon before DMF (2.0 mL) was injected using a syringe. Afterwards the Schlenk tube in the ice bath was degassed by evacuation and backfilling with argon three times. The reaction mixture was then stirred for 12 h at 120 °C. After the reaction was complete, the reaction mixture was diluted with H_2O (5 mL), extracted with EtOAc (3 × 10 mL) and dried with anhydrous Na_2SO_4. After filtration and addition of silica gel into the solution, the organic solvent was reduced evaporated. The crude product was purified by column chromatography using EtOAc–*n*-pentane.
Xanthenone (**3a**)
White solid; yield: 74.5 mg (76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (2 H, ddd, *J* = 8.0, 1.7, 0.5 Hz), 7.73 (2 H, ddd, *J* = 8.7, 7.1, 1.8 Hz), 7.52–7.48 (2 H, m), 7.38 (2 H, ddd, *J* = 8.1, 7.1, 1.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.27, 156.20, 134.86, 126.77, 123.94, 121.88, 118.02. GC–MS (EI, 70 eV): *m/z* (%) = 196 (100), 168 (75), 139 (58), 113 (6), 92 (8), 74 (11), 63 (20). HRMS (EI): *m/z* calcd for $C_{13}H_8O_2$ $[M]^+$: 196.05188; found: 196.05185.
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