Regioselective Synthesis of 4-Substituted-1-Aryl-1-butanones Using a Sonogashira-Hydration Strategy: Copper-Free Palladium-Catalyzed Reaction of Terminal Alkynes with Aryl Bromides[1]

Manojit Pal,* Karuppasamy Parasuraman, Shalabh Gupta, Koteswar Rao Yeleswarapu

Chemistry-Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500050, India
Fax +91(40)3045438 ; E-mail: manojitpal@drreddys.com

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Abstract: A simple one-pot procedure has been developed for the synthesis of 4-substituted-1-aryl-1-butanones through copper-free Sonogashira reaction of aryl bromides with terminal alkynes in DMF under inert atmosphere, followed by the treatment with acid in the presence of oxygen. A variety of aryl bromides was reacted with 3-butyn-1-ol according to this procedure to give the expected compounds in good yield. The mechanism of the reaction and applications of the methodology are discussed.

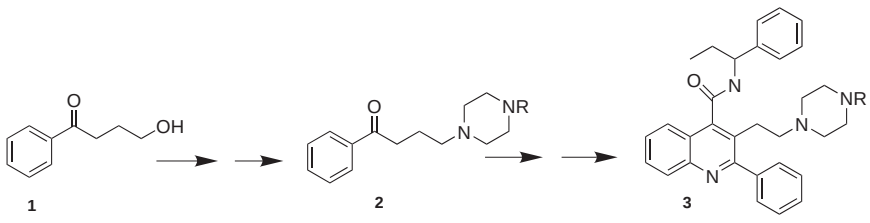
Key words: 1-aryl-1-butanones, aryl bromide, 3-butyn-1-ol, palladium catalyst, hydration

1-Aryl-1-butanones of the structure $ArCOCH_2CH_2CH_2Z$ [**I**, where Ar and Z are (hetero) aryl and hydroxy, halo etc. respectively] are extremely useful intermediates[2] needed for various synthetic strategies, especially for the preparation of agrochemicals and drugs. This is exemplified by their use in the preparation of biologically active compounds such as 2-(ω-aroylalkyl)-4-biaryloxobutyric acids as matrix metalloprotease inhibitors[3] for tumor cell invasion and angiogenesis or 2-(3-aryloxy/aroylpropyl)amino-1,3-thiazoles[4] as anti-inflammatory agents or naphthothiazole-substituted piperidine derivatives[5] as inhibitors of stomach acid secretion. They are also useful precursors for the preparation of quinoline-4-carboxamide derivatives (**3**, Scheme 1) as NK2 and NK3 receptor antagonists[6] for the treatment of asthma.

In view of the importance of 1-aryl-1-butanones, a number of methods have been developed for their synthesis[7–11]including the use of transition metal complexes.[12] Amongst the various methods reported for the preparation of **1** (**I**, Ar = C_6H_5, Z = OH), the most straightforward involves the reaction of nucleophilic aryl lithium with electrophilic lactone carbonyl moiety of γ-butyrolactone followed by treatment with ammonium chloride.[13] Although the method has been utilized successfully for the preparation of compounds having biological importance,[6] the protocol suffers from several limitations, the most important being the difficulties in the preparation of organolithium reagents when applied to more complex systems (especially in the presence of an acidic functional group).

As a part of our current research program directed toward the synthesis of compounds for biological testing in different therapeutic areas,[14] we required a simple procedure for the synthesis of a variety of 1-aryl-1-butanones **1**. Since the existing routes to obtain **1** were either inappropriate (due to the non-availability of the required starting material) or unattractive due to the complicated synthetic procedure we therefore became interested to develop an alternative method for the synthesis of **1**. Our synthetic strategy, which relied on umpolung[15] of the usual reactivity pattern associated with the earlier method [7a–d,13] is shown in Scheme 2.

Of the variety of transition-metal mediated reactions, Sonogashira coupling reaction of aryl halides with terminal acetylenes provides a powerful tool for C–C bond formation.[16] This palladium–copper-catalyzed reaction is typically carried out in the presence of catalytic amounts of a palladium(II) complex as well as copper(I) iodide in an amine as solvent. Although extensive applications of Sonogashira coupling of aryl iodides (as the order of halide reactivity is I > Br >> Cl) with terminal alkynes have been reported in the literature since 1975, effective use of aryl bromides[17] has only recently been explored.[18] Thus



Scheme 1 Synthesis of quinoline-4-carboxamides as NK2 and NK3 receptor antagonists.

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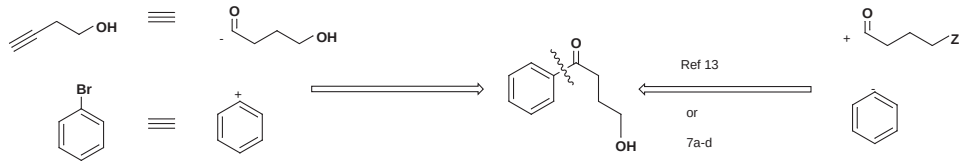
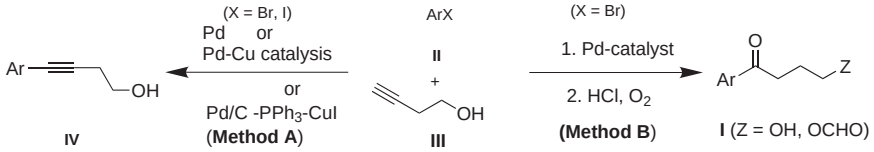


Scheme 2 Synthetic strategy for the preparation of **1**.

Krause et al. reported an improved procedure for the coupling of aryl bromides, which are less expensive and easy to prepare compared to aryl iodides, with terminal alkynes using THF as solvent.[18a]Use of an efficient catalyst i.e. $Pd(PhCN)_2Cl_2/P(t\text{-}Bu)_3$ for Sonogashira reactions of aryl bromides has been reported by Buchwald and et al. very recently.[19] Although substantial improvement in reaction conditions has been observed in these cases, all these procedures require the use of variable amounts (2–4 mol%) of copper(I)iodide for efficient coupling. It is well known that dimerization of terminal alkynes to the corresponding diyne is often a side reaction under the Sonogashira coupling conditions[18,20] and this oxidative homocoupling (Glaser coupling) predominates[21] in the presence of oxygen or other reagents. CuI in the presence of excess amine base seemed to have a significant role in such oxidative homocoupling of terminal acetylenes. Since the separation of diynes from the desired product is often cumbersome, copper-free Sonogashira reactions[22] have significant advantages over the original method. Very recently Ryu et al. reported a copper-free Sonogashira coupling of aryl iodides with terminal alkynes in an ionic liquid.[22a]To the best of our knowledge, however, only few descriptions of copper-free Sonogashira coupling employing aryl bromides are available in the literature[17a,17c–d,17h–i] and none of them describe the use of electron rich or unactivated[19] aryl bromides. Use of dimethylformamide (DMF) as a co-solvent for efficient Sonogashira reaction (especially where the aryl halide is insoluble in other solvent) is not very common.[16c] In this connection we have observed that DMF could be utilized as an effective solvent for the synthesis of compounds of potential biological interest via Sonogashira-hydration strategy. We thought this process could be a means to promote the equivalent of a Friedel–Crafts acylation reaction[7a–d]of deactivated aryl derivatives, which is a demanding transformation and is not readily achieved even in the presence of most effective Lewis acid catalysts. Herein, we disclose regioselective one-pot synthesis of **I** via copper-free Sonogashira coupling of aryl bromides with a terminal alkyne in DMF followed by in situ hydration of the resultant alkyne in the presence of palladium catalyst and atmospheric oxygen in aqueous acid.

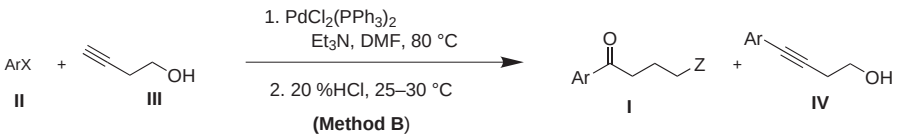
When aryl halide (**II**, X = Br, I) was treated with 2 equivalents of 3-butyn-1-ol (**III**) in DMF in the presence of $PdCl_2(PPh_3)_2$ (0.03 equiv) and triethylamine (8 equiv) under nitrogen atmosphere at 80 °C for 8 hours, 4-aryl-3-butyn-1-ol (**IV**, Method A, Scheme 3) was obtained in good yield. However, we have observed that 1-aryl-1-butanones (**I**, Ar = substituted aryl group, Z = OH or OCHO) were formed as the major product when the same reaction was performed using aryl bromides followed by the treatment with 20% hydrochloric acid in the presence of aerial oxygen for 8 hours at 25–30 ºC in the same pot (Method B, Scheme 3). Our results are summarized in Table 1.

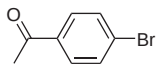
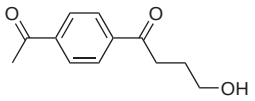
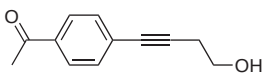
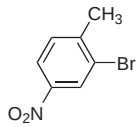
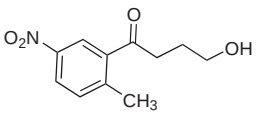
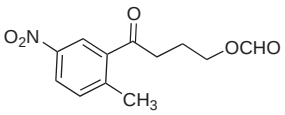
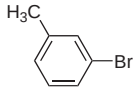
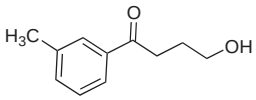
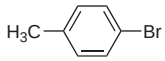
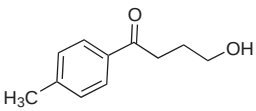
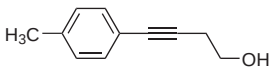
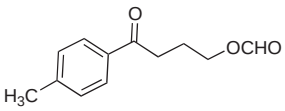
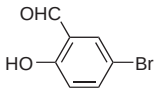
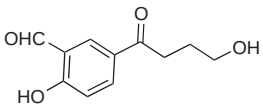
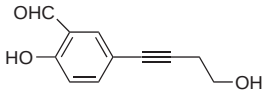
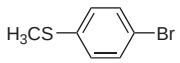
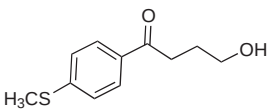
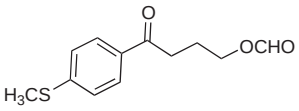
By use of this tandem coupling-hydration protocol a wide variety of butanones have been prepared (Table 1).[23] Thus 3-butyn-1-ol was reacted with an array of commercially available aryl bromides bearing a variety of substituents (Table 1, Entries 1, 4, 6, 7, 9, 10) e.g. either electron donating (Me, SMe) or withdrawing groups ($COCH_3$, NO_2, CHO) and all these substituents were well tolerated in this single pot reaction. Hydroxyketone **I** was isolated as the major product in most of the cases along with the internal alkyne **IV** in a few cases (Entries 1, 7, 9). However, the nature of the product (**I** or **IV**) formed in this coupling-hydration protocol was affected by the duration of the treatment with acid (Entry 1, Step 2, Table 1) and **I** was isolated as the major product when the hydration (Step 2) was carried out for 8 hours. Further increase in time in Step 2 led to the generation of product that seemed to resulted from O-formylation of the hydroxy ketone **I** (Entry 5, 8, 11, Table 1). It is pertinent to note that no oxidative homocoupled product of terminal alkynes was detected in all these cases. Another important point to note about the present coupling-hydration protocol is the regiospecific formation of ketone (Entry 6 vs 7, Table 1). Since the alkynylation occurs only at the bromine bearing carbon of the aromatic ring therefore, whilst the electronic effects (resonance and inductive) may influence the rates of the reactions, as a consequence of Pd-mediated reaction



Scheme 3 Palladium-catalyzed coupling of 3-butynol with aryl halides.

Table 1 Synthesis of 1-Aryl-1-butanones (**I**)[a]



Entry	ArX (**II**)	Products[b] **I**	**IV**	Time (h) Step 1	Step 2	% Yield[c] **I**	**IV**
1	 **IIa**	 **Ia**	 **IVa**	8	8	59	16
2	**IIa**	n.d.[e]	**IVa**	8	8	–	89d
3	**IIa**	n.d.	**IVa**	8	1	–	84
4	 **IIb**	 **Ib**	n.d.	8	8	44	21
5	**IIb**	 **Ibb**	n.d.	8	16	47	–
6	 **IIc**	 **Ic**	n.d.	8	8	56	–
7	 **IId**	 **Id**	 **IVd**	8	8	46	13
8	**IId**	 **Idd**	n.d.	8	16	43	–
9	 **IIe**	 **Ie**	 **IVe**	8	8	37	19
10	 **IIf**	 **If**	n.d.	8	8	61	–
11	**IIf**	 **Iff**	n.d.	8	16	55	–

[a] Reactions were carried out by using **II** (1.0 equiv), **III** (2.0 equiv), $PdCl_2(PPh_3)_2$ (0.03 equiv), Et_3N (8 equiv) in DMF. [b] Identified by ^1H NMR, IR, Mass.
[c] Isolated yields.
[d] Reaction was performed using Pd/C:PPh_3:CuI, 1:4:2, 2.5 equivalents of 3-butyn-1-ol in DME:H_2O (see Ref.[17g]).
[e] n.d. = not detected.

directing the key transformation, the composition of ketone remains unaffected by the nature and the position of substituent in the starting bromide. This is in sharp contrast to the result using Friedel–Crafts acylation reaction where reactivity and orientation of electrophilic substitution reaction is influenced by the nature of the group present in the starting aromatics.

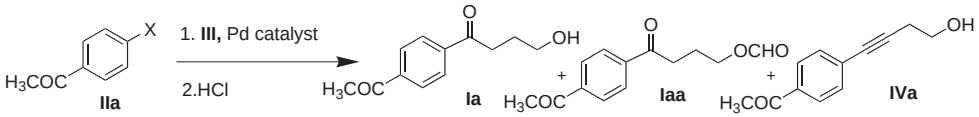
The copper-free Sonogashira coupling was carried out in DMF using triethylamine as a base. The advantage in the use of DMF as solvent is its ability to solubilize a wide variety of aryl bromides and palladium catalysts as well as its miscibility with aqueous HCl and therefore facilitates the coupling-hydration reaction well. However, the use of other solvents such as THF and dioxane was also investigated and was found to be less effective in terms of yield.

The coupling reaction (Step 1) was usually carried out at 80 ºC whereas hydration of the resultant alkyne (Step 2) proceeded well at 25–30 ºC. The effect of temperature, time, catalyst and the nature of aryl halide used on product distribution are summarized in Table 2. Lowering of reaction temperature in Step 1 completely suppressed the product formation (Entry 1, Table 2) confirming the need of higher temperature for the conversion of Pd(II) to Pd(0). Although the increase in time in Step 2 altered the product distribution drastically (Entry 2 vs 3, Table 2) the conversion rate however, remained unaffected even after further increase in time (Entry 2-4, Table 2). Quantitative conversion was achieved using aryl iodide in place of aryl bromide but in this case, alkyne was isolated as the major product under identical reaction conditions (Entry 5, Table 2). Appearance of a palladium mirror on the wall of the reaction flask in this case may offer an explanation for such observation.[24a]

The coupling-hydration method proceeded well in the presence of $PdCl_2(PPh_3)_2$ as catalyst leading to the formation of the ketone **I** as major product in most of the cases. Use of other catalysts such as $Pd(PPh_3)_4$ was also investigated and was found to be less effective (Entry 5, Table 2) implicating the better efficacy of Pd(0) complex generated in situ in the present case. Interestingly, bromobenzene in the presence of $Pd(PPh_3)_4$-NaOMe catalyst system, when treated with terminal alkyne, afforded biphenyl in low yield instead of desired alkyne.[22b] No rearranged product was detected when the catalyst system $PdCl_2(PPh_3)_2$-Et_3N (Method B) was replaced by 10% Pd/C-PPh_3-CuI-K_2CO_3 (Method A)[17g] and normal coupled product was isolated in good yield (entry 2, Table 1) even after treatment with 20% HCl solution for 8 hours in the presence of air. However, to gain further evidence on the nature of the hydration reaction, the isolated alkyne[24b] was treated separately with 20% HCl at 25–30 ºC but no significant change was observed even after stirring for 3 days in open air and 80% of the reactant alkyne was recovered. Hydration of a triple bond is a well-known reaction,[25] which is catalyzed by Hg salts, its Nafion modification, or strong acid such as H_2SO_4, trifluoromethanesulfonic acid or trifluoromethanesulfonimide[25a] in the presence of water. However, hydration in the presence of HCl at room temperature is not known in the literature whereas palladium-catalyzed hydration of alkyne is a known process.[26] Thus literature reports as well as our observations indicate that the palladium complex present in the reaction mixture has a significant role in the hydration of the resultant alkyne when exposed to acid and air simultaneously.

The Sonogashira coupling-hydration reaction was found to be highly regioselective in view of product formation as only 1-aryl-1-butanones (**I**) and no other regioisomers were detected under the reaction conditions employed. All the products isolated were well characterized by their ^1H NMR, Mass and IR spectra (carbonyl stretching frequencies in the region of 1690–1670 cm^{-1}).

Table 2 Effect of Reaction Conditions on Product Distribution[a]



Entry	X	Catalyst	Condition [T (ºC); t (h)]		Conv.[b] (%)	Product Distribution[c] (%)		
			Step 1	Step 2		**Ia**	**Iaa**	**IVa**
1	Br	$Pd(PPh_3)_2Cl_2$	35–40; 8	–	0	–	–	–
2	Br	$Pd(PPh_3)_2Cl_2$	80; 8	20–30; 8	>80	59	n.d.[d]	16
3	Br	$Pd(PPh_3)_2Cl_2$	80; 8	20–30; 16	>85	19	51	n.d.
4	Br	$Pd(PPh_3)_2Cl_2$	80; 8	20–30; 24	>80	12	55	n.d.
5	I	$Pd(PPh_3)_2Cl_2$	80; 8	20–30; 8	100	10	n.d.	70
6	Br	$Pd(PPh_3)_4$	80; 8	20–30; 8	>50	–	–	39

[a] Reactions were carried out by using **II** (1.0 equiv), **III** (2.0 equiv), $PdCl_2(PPh_3)_2$ (0.03 equiv), Et_3N (8 equiv) in DMF.
[b] Conversion was determined on the basis of the isolated yield of product and recovered starting material.
[c] Product distributions were calculated based on the isolated yield of each product.
[d] n.d. = not detected.

The mechanism of the reaction could be envisaged as shown in Scheme 4. The alkyne **IV** generated via usual palladium(0) [generated from palladium(II)complex]-catalyzed[27a,b] coupling of aryl bromide **II** with 3-butyn-1-ol **III** subsequently participates in Pd(II) mediated hydration reaction. Generation of Pd(II) from Pd(0) is catalyzed by molecular oxygen[27c–d] in the presence of Et_3NHX. Participation of the terminal hydroxyl group of the resultant alkyne during the hydration process seemed to have the key role in the formation of a particular regioisomer.[28] The Pd(II)-alcoholate **V**[22b] thus formed may lead to the formation of ketone **I** (when quenched with excess water) or formylated product **VI** (when allowed to stir for longer period in DMF–HCl)[29] depending on the reaction conditions employed. Further study on this mechanistic sequence is in progress.

We have demonstrated that a variety of 1-aryl-1-butanones (**I**), having a substituent (especially hydroxy) at the 4-position, can be synthesized via palladium-catalyzed alkynylation of aryl bromides followed by subsequent hydration of internal alkynes generated in situ. This is worthwhile in comparison to other one-pot reactions (e.g. $SnCl_2$–EtOH–H_2O or Fe–NH_4Cl–CH_3COOH as reductive hydrating agent) where hydration of acetylene moiety was found to be inconsistent.[25d] Notably, regioselectivity of the triple bond hydration in the present case was not affected by the nature of the aryl group attached to it.[25e] Thus the present Sonogashira-hydration technique represents a general and versatile method for the synthesis of **I** and offers a significant tactical advantage over traditional Lewis acid-catalyzed acylation reactions. The methodology has been utilized for the synthesis[30] of compounds of potential biological interest.[6,30a,b] Compound **1d** was converted to **VI**, which is known to be useful for the treatment of atherosclerosis via raising the level of HDL cholesterol,[31]according to the known procedure (Scheme 5).[30b] Compound **1a** was converted to the corresponding bromide, which is useful precursor for the synthesis of potential antipsychotic agents, using the reported method.[32]

To conclude, the present communication deals with a convenient one-pot procedure for the regioselective synthesis of 1-aryl-1-butanones. To the best of our knowledge this is the first example for the synthesis of 1-aryl-1-butanones employing such a methodology. The method involves the use of readily available aryl bromides in the absence of copper salts, thereby preventing the formation of diynes as side product. Due to the mild reaction conditions and functional group tolerability the present protocol is certainly superior to the existing methods, particularly in that it allows the regiospecific functionalization of the activated and deactivated aromatics to afford substituted butanones having a wide range of aryl residues. More importantly the present protocol is safer than other methods, which involve use of pyrophoric organolithium reagent or environmentally harmful $AlCl_3$, or toxic Hg salts. The methodology has been utilized for the preparation of compounds of biological interest and its further application in organic synthesis is presently under investigation.

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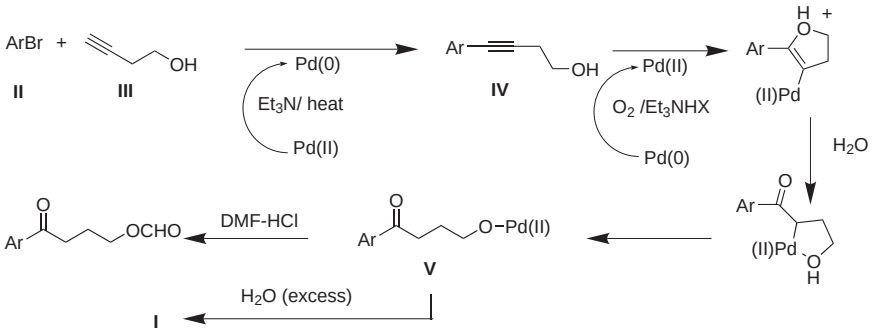
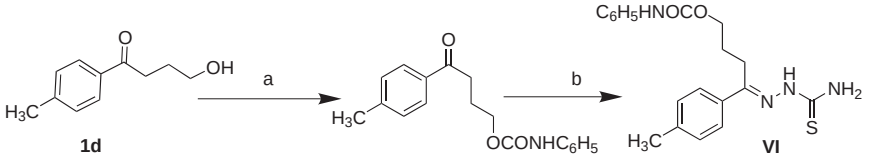


Scheme 4 Mechanism of the base promoted oxidative cyclization reaction.



Scheme 5 *Reagents and conditions*: a) C_6H_5NCO, Et_3N, C_6H_6, 80 °C, 4 h; b) $NH_2NHC(S)NH_2$, MeOH, 1 N HCl, 25 °C, 24 h.

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(23) **Typical procedure for the synthesis of 4-substituted 1-aryl-1-butanones**: Preparation of **Ia**: To a solution of 4-bromoacetophenone (1 g, 5.03 mmol) in DMF (10mL) was added $PdCl_2(PPh_3)_2$ (0.10 g, 0.15 mmol)and Et_3N (4.06 g, 40.20 mmol) under nitrogen atmosphere. The mixture was stirred for 15 min at 25 C and then 3-butyn-1-ol (0.71 g, 10.05 mmol) was added very slowly via syringe to the stirred reaction mixture. The temperature of the mixture was increased slowly to 80 °C and stirring continued for 8 h. During the reaction, which was followed by TLC, precipitation of $Et_3N{\cdot}HBr$ as crystalline solid was observed. After the complete consumption of the aryl bromide, the reaction mixture was cooled to r.t. and 20% HCl solution (100 mL) was added to it with vigorous stirring. After stirring for 8 h the mixture was diluted with water and EtOAc (150 mL), filtered through a small pad of celite (EtOAc). The organic layer was collected, washed with H_2O (2×100 mL), dried over anhyd Na_2SO_4, filtered and concentrated under low vacuum. The residue thus obtained was purified by flash chromatography to afford the desired compound. Compound **Ia** was isolated in 59% yield as light yellow solid, mp 91–92 °C (hexane); IR (KBr): 3342 (br, OH), 1678 (C=O), 1502 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.04 (m, 4 H, ArH), 3.76 (t, J = 5.91 Hz, 2 H, CH_2OH), 3.16 (t, J = 6.98 Hz, 2 H, CH_2CO), 2.65 (s, 3 H, CH_3), 2.09–1.97 (m, 2 H, CH_2), 1.65 (br s, D_2O exchangeable, 1 H, OH); M (CI, I-butane): m/z (%) = 207 (100) [MH^+]; ^{13}C NMR: 199.89, 197.61, 139.94, 139.87, 128.37 (2 C), 128.13 (2 C), 61.71, 35.42, 26.74, 26.62.
Spectral data for **1d**: pale yellow oil; IR (KBr): 3420 (br, OH), 1679 (C=O), 1607 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.81 Hz, 2 H, ArH), 7.29 (d, J = 7.80 Hz, 2 H, ArH), 3.76 (t, J = 5.86 Hz, 2 H, CH_2OH), 3.13 (t, J = 6.84 Hz, 2 H, CH_2CO), 2.43 (s, 3 H, CH_3), 2.09–1.97 (m, 2 H, CH_2), 1.80 (br s, D_2O exchangeable, 1 H, OH); MS (CI, I-butane): m/z (%) = 179 (100) [MH^+]; ^{13}C NMR:

199.12, 143.87, 134.27, 129.20 (2 C), 128.15 (2 C), 62.28, 35.21, 27.00, 21.64.
Spectral data for **1ff**: IR (KBr): 1719 (OCHO), 1665 (C=O), 1588 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.07 (s, 1 H, CHO), 7.88 (d, *J* = 8.33 Hz, 2 H, ArH), 7.27 (d, *J* = 8.30 Hz, 2 H, ArH), 4.28 (t, *J* = 6.31 Hz, 2 H, CH_2O), 3.05 (t, *J* = 7.13 Hz, 2 H, CH_2CO), 2.53 (s, 3 H, SCH_3), 2.16–2.09 (m, 2 H, CH_2); MS (CI, I-butane): *m/z* (%) = 239 (100) [MH^+].

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