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ARTICLE

Ruthenium-catalysed *C*-alkylation of 1,3-dicarbonyl compounds with primary alcohols and synthesis of 3-keto-quinolines

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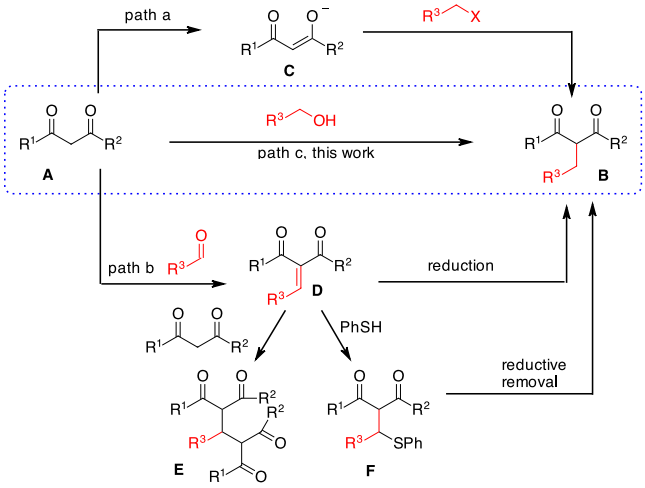
The mono-alkylation of 1,3-diketones using alcohols is possible in the presence of catalytic amounts of $Ru(CO)(PPh_3)_3HCl$ and 10% mol of the Hantzsch ester. The borrowing hydrogen process between the catalyst and the dihydropyridine/pyridine couple prevents the common double alkylation of the Knoevenagel adduct without the need of stoichiometric reducing agents or sacrificial nucleophiles. The reaction was applied to the synthesis of a lactone intermediate for the preparation of the anti-obesity drug Orlistat. Moreover, under the same Ru catalysis, a Friedländer reaction occurred with *o*-amino benzyl alcohols giving access to different 3-keto-substituted quinolines.

Introduction

The functionalization of activated methylene compounds, including 1,3-diketones, is one of the most important synthetic techniques for carbon-carbon bond formation. The standard procedure for alkylation is the reaction of the anion, derived from the 1,3-dicarbonyl compound, with alkyl halides (Scheme 1, path a). Alternatively, a Knoevenagel-Doebner reaction with aldehydes followed by carbon-carbon double bond reduction is possible (Scheme 1, path b). Nowadays, these two methodologies require to be replaced by more efficient processes. Alkylation works under highly basic conditions and employs toxic and mutagenic alkyl halides. On the other hand, depending on the substrate nature, the Knoevenagel-Doebner process leads to poor yield. The intermediate conjugated alkene **D** is indeed a good Michael acceptor capable of engaging the unreacted dicarbonyl reagent **A** in a kinetically rapid 1,4-addition to give the bis-adduct **E**.[1] To avoid this side reactions two possible strategies are: i) slow addition of the β-diketone to a mixture of the aldehyde and a reducing agent (stoichiometric amount) in order to keep low the concentration of **D** so that the Michael addition will occur more slowly in comparison with the reduction of the Knoevenagel alkene;[2] ii) use of stoichiometric amount of strong nucleophiles (*i.e.* thiols, $NaSO_2Ph$, primary amines) to intercept **D** before forming the bis-adduct **E**.[1,3] In this case, a further step of reduction to remove the sacrificial nucleophile is required.

Unquestionably, the alkylation of *β*-dicarbonyl compounds with an alcohol would provide an attractive salt-free, environmentally friendly and atom-economic alternative to known protocols (Scheme 1, path c).

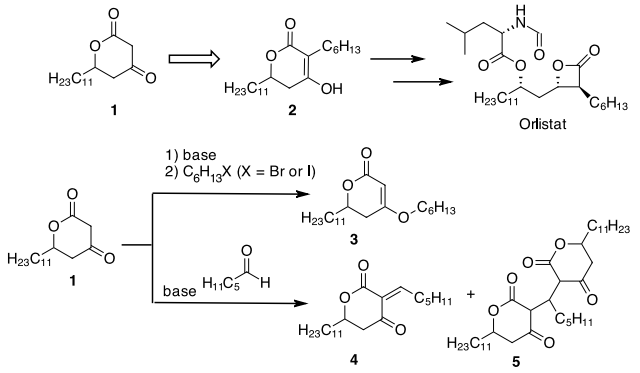


Scheme 1 Possible pathways to prepare 2-alkylated 1,3-diketones

Recent demonstrations of Lewis and Brønsted acid catalysed alkylation of 1,3-dicarbonyl compounds with benzyl-, allyl- and propargyl- alcohols have been reported.[4] However, these procedures often suffer from low versatility being the alcohol scope limited to the very reactive substrates previously mentioned. A valuable alternative is the metal catalysed alkylation with alcohols through the red-ox 'borrowing hydrogen'[5–7] strategy that has been already successfully applied to ketonitriles,[8,9] and cyanoacetates.[10]

Engaged in a total synthesis of Orlistat, a powerful gastrointestinal lipase inhibitor contained in anti-obesity drugs, we were interested in a suitable protocol for the preparation of

key intermediate lactone **2** (Scheme 2).[11,12] Unfortunately, direct base mediated alkylation of **1** produced a mixture of compound **2** and *O*-alkylated enol ether **3**. Attempts to react hexanal with **1** gave almost exclusively the bis-adduct **5**. Consequently, the investigation of a possible alkylation of 1,3-dicarbonyl compounds with primary alcohols in the presence of homogeneous Ru catalysts was investigated (Scheme 1, path c).

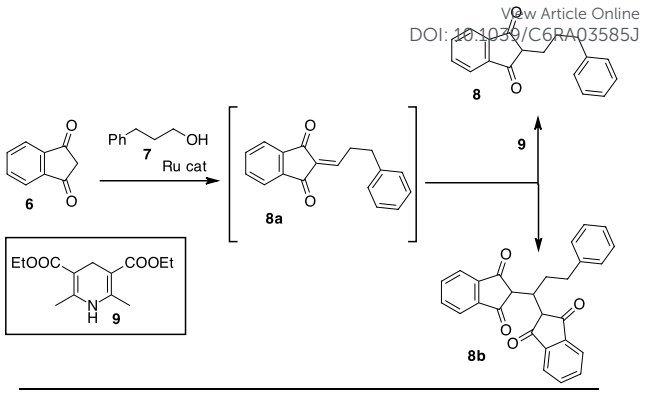


Scheme 2 Attempts to prepare a key intermediate for the total synthesis of Orlistat.

Results and discussion

Initially, in order to find the best reaction conditions, 1,3 indandione **6** was chosen as a model substrate for the more valuable lactone **1**, while 3-phenyl-1-propanol **7** was selected as a UV visible non-benzylic alcohol. These starting materials were heated under different conditions in the presence of ruthenium-based catalytic species obtained by mixing different ruthenium precursors, sometimes using Xantphos as the ligand (Table 1). Mixing the two starting materials dissolved in toluene in the presence of $Ru_3(CO)_{12}$ or [Ru(*p*-Cymene) $Cl_2]_2$ with or without Xantphos, the expected compound **8** was formed in low yields, most of the starting material remaining unchanged (Table 1, entry 1-3). [Ru(CO)$(PPh_3)_3$HCl] turned out to be the best catalyst providing product **8** in moderate yields even without the addition of Xantphos as the ligand (Table 1, entries 4-5). High temperature (160 °C) was always required for the transformation, as only traces of product were observed in refluxing toluene (Table 1, entry 6). No improvements were achieved by using different amounts of **6** or **7** (Table 1, entries 7-8), changing solvents (Table 1, entries 9-12), under microwave dielectric heating (Table 1, entry 13) or by using 1 eq of base (Table 1, entry 14, other bases different from *t*-BuOK that gave no trace of product **8** are not quoted in the Table). In any of the attempted reactions, the main by-product was the bis-adduct **8b** suggesting that the hydrogen extracted by the ruthenium catalyst reduced the Knoevenagel alkene **8a** too slowly respect to the kinetic of the Michael addition. The addition of Hantzsch ester (**9**) in order to increase the efficiency of the reductive step[13–15] was then investigated observing a substantial increase of the yields and the disappearance of the dimer (Table 1, entry 15).

Table 1 Optimization of reaction conditions



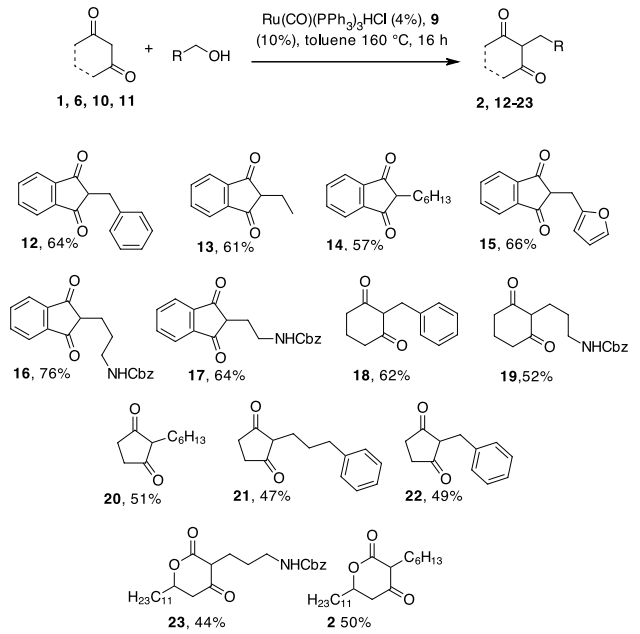
Entry	Ru Catalyst	Reaction Conditions[a]	**8**[b](%)
1[c]	$Ru_3(CO)_{12}$	Toluene, 160 °C	21
2	$Ru_3(CO)_{12}$	Toluene, 160 °C	-
3[c]	[Ru(*p*-Cymene) $Cl_2]_2$	Toluene, 160 °C	18
4[c]	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, 160 °C	20
5	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, 160 °C	23
6	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, reflux 24 h	<5
7[d]	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, 160 °C	25
8[e]	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, 160 °C	22
9	[Ru (CO)$(PPh_3)_3$HCl]	Dioxane 160 °C	22
10	[Ru (CO)$(PPh_3)_3$HCl]	THF 160 °C	15
12	[Ru (CO)$(PPh_3)_3$HCl]	TAA, 160 °C	19
13	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, MW 160 °C, 1 h	<5
14	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, *t*-BuOK (1 eq), 160 °C	15
15	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, 160 °C, **9** (1 eq)	58
16	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, 160 °C, **9** (0.5 eq)	57
17	[Ru (CO)$(PPh_3)_3$HCl]	Toluene, 160 °C, **9** (0.1 eq)	58

[a] Reaction conditions: **6** (0.5 mmol), **7** (0.5 mmol), catalyst (4 mol%) in solvent (1 mL) under nitrogen, sealed vial at 160 °C for 16 h. b) Yields of pure product isolated by flash chromatography [c] Xantphos (6 mol%). [d] 3 eq of **6** [e] 3 eq of **7**.

As in principle the Hantzsch ester could be regenerated during the overall process, we explored the reaction in the presence of catalytic amounts of **9**, founding that 10% molar was enough to carry out the transformation without affecting isolated yields of **8 (**Table 1, entries 16-17).

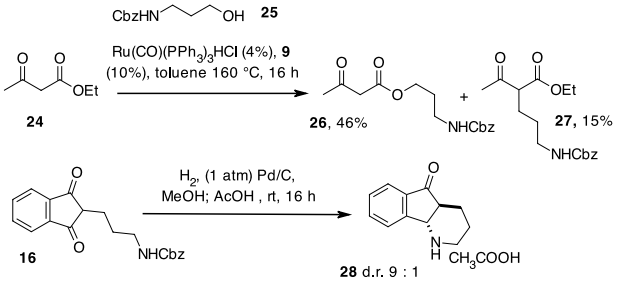
The scope and generality of the overall process was further examined by treating different 1,3-dicarbonyl compounds with several primary alcohols carrying different functional groups under the previously optimized reaction conditions. A series of alkylated 1,3-dicarbonyl compounds was obtained in moderate to good yields as shown in Scheme 3. In any case, in the crude reaction mixture we observed different amounts of the starting 1,3-diketones and, with compounds **11** and **12**, small amounts of the O-alkylated products (< 5%). The mono-alkylation products obtained from 1,3 indandione **6** are formed in higher yield with respect to the products derived from the simple 1-3-cyclohexandione **10** or 1,3-cyclopentandione **11**, suggesting probably a (stereo)electronic effect of the aromatic ring. The remarkable effect of the cyclic 1-3 dicarbonyl compound on the

reaction was confirmed by the observation that no reaction occurred with acyclic 1,3-diketones as acetylacetone or 1-phenyl-1,3-butandione.



Scheme 3. Alkylation of 1,3-dicarbonyl compounds with alcohols: reaction scope. **10** = 1,3-cyclohexandione; **11**= 1,3-cycopentandione.

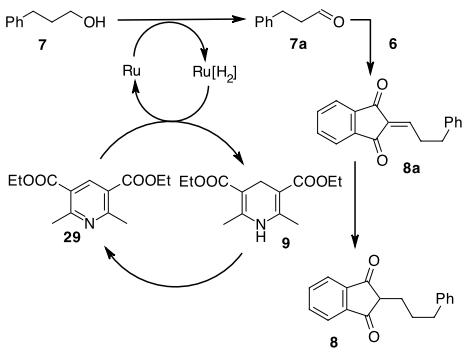
Carbamates are well tolerated by this transformation giving previously unreported Cbz protected amino diketones **16-17** in satisfactory yields. Also lactone **1** was alkylated in acceptable yields giving the amino derivative **23** and also the Orlistat intermediate **2** was obtained in 50% isolated yields (Scheme 3). However, using acyclic β-keto esters such as ethyl acetoacetate or even *t*-butyl acetoacetate, the product coming from a transesterification reaction between the alcohol and the ester was formed in large amounts. Only using the *N*-Cbz-3-amino-1-propanol **25** a moderate amount of the alkylated product **27** was obtained, although the transesterification derivative **26** was again the major product (Scheme 4).



Scheme 4. Reaction with acyclic β-keto esters and Cbz removal followed by intramolecular reductive amination.

Probably the result observed on this substrate can be related to a coordinative effect of the carbamate on the ruthenium catalyst. To investigate the synthetic potential of the new Cbz derivatives synthesized, the removal of Cbz was attempted. Treating **16** with H_2 and Pd/C in AcOH a domino deprotection reductive amination occurred to form the tricycic 3,4,4a,9b-tetrahydro *H*-indeno[1,2-*b*]pyridine-5-one 29 (Scheme 4). This new product,[16] obtained as a 9:1 diastereomeric mixture after 16 h of reaction, was isolated as a single diastereomer in 47% yield after purification by flash chromatography. Finally, using secondary alcohols (e.g. 2-propanol or cyclopentanol), very low yield of the alkylated product was obtained.

For this Ru catalysed mono-alkylation of 1,3-diketones mediated by catalytic amount of the Hantzsch ester, a possible mechanism was hypothesized (Scheme 5). The alcohol **7** is oxidized by the Ru catalyst[17] to the corresponding aldehyde **7a** that reacts with the β-diketone **6** to give the Knoevenagel product **8a**. The conjugated alkene is then reduced to the monolakylated 1,3-dicarbonyl compound **8** by the Hantzsch ester,[14] while the contemporary formed pyridine **29** is reduced again by the Ru[H_2], regenerating the Hantzsch ester **9** and the Ru catalyst. Thus, through this double borrowing hydrogen process between the alcohol and the couple dihydropyridine/pyridine, a catalytic alkylation of β-diketones with alcohol is possible.



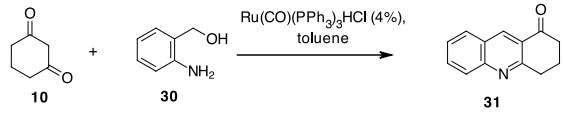
Scheme 5. Possible mechanism.

The potential use of *o*-amino-benzyl alcohol **30** with 1,3-diketones (as **10**) was investigated in order to explore the possibility of a ruthenium catalysed Friedländer cyclisation (Table 2). Although modified quinoline synthesis *via* ruthenium-catalysed coupling of 2-aminobenzyl alcohols and 2-nitrobenzyl alcohols with alcohols or ketones has been previously reported,[18–25] to our knowledge, the only example of 3-carbonyl-quinolines synthesis involves the reaction of β-keto esters with formation of α-carbocation intermediate generated by the red-ox catalytic couple $FeCl_3$ / $SnCl_2$.[26]

In the reaction conditions explored so far, condensation of **10** with **30** gave the 3,4-dihydro 1(*2H*)-acridone **31** in 70% yield (Table 2, entry 1). In order to increase the yield of the pursued approach, different reaction conditions were explored. First of all, the influence of the temperature was investigated. Lowering the reaction temperature to 120 °C, the yield dropped down to

57% (Table 2, entry 2). However, the reaction works beautifully under microwave dielectric heating without the Hantzsch ester (Table 2, entries 3-6). After 30 minutes at 120 °C compound **31** was isolated in 73 % yield (Table 2, entry 6).

Table 2 Optimisation of the Ru catalysed Friedländer reaction



Entry	Conditions[a]	Yield(%)
1	160 °C, 16 h	70
2	120 °C, 16 h	57
3	MW, 160 °C, 15 min	43
4	MW, 120 °C, 15 min	53
5	MW, 80 °C, 15 min	41
6[b]	MW, 120 °C, 30 min	73
7	Cyclohexene (10 eq.), MW, 120 °C, 30 min	55
8	Crotonitrile (10 eq.), MW, 120 °C, 30 min	42
9	MW, 120 °C, 30 min	57
10	MW, 120 °C, 30 min	51
11	KOH (1 eq.), MW, 120 °C, 30 min	47
12	*t*-BuOH (1 eq.), MW, 120 °C, 30 min	52

[a] **10** (1 eq), **30** (1 eq), catalyst (4% mol), [bmim][BF_4] (25µl), toluene (1 mL) [b] 2 eq. of ketone

Unexpectedly, using the two different hydrogen acceptors cyclohexene (Table 2, entry 7) and crotonitrile (Table 2, entry 8) the yield did not improve while still traces of reduced by-products were present. The reaction is supposed to follow the standard Ru catalysed Friedländer mechanism including a last oxidative step done by air.[18] Once established the best reaction conditions, different 1,3-dicarbonyl compound and 2-aminobenzyl alcohols were examined to explore the generality of the protocol (Table 3). It is possible to carry out the reaction with *o*-substituted amino-benzyl alcohols or in the presence of an aryl chloride (Table 3, entries 1-2). The reaction worked well with 1,3-cyclopentandione (**11**), 1,3-cyclohexanediones **10** and **34**, and indandione **6** (Table 3, entries 3-5). It was worth noting that even linear diketones such as **35** and **36** gave the 3-ketoquinolines in acceptable yields (Table 3, entries 6-7). In the case of not symmetrical diketone **36**, the quinolone **43** was the only product isolated. The identity of **43** was established by comparison with reported data.[27] Analogously, keto lactone **1** gave the quinolone lactone **44** in acceptable yield.

Conclusions

In summary, we have developed an hydrogen borrowing process for a direct α-alkylation of β-dicarbonyl compounds using alcohols instead of toxic alkyl or benzyl halides. The contemporary use of ruthenium and Hantzsch ester catalysis prevents the formation of the Michael addition by-product without using stoichiometric amounts of reducing agents or sacrificial nucleophiles. The yield of the final products strongly depends on the ketones and the alcohols nature, obtaining quinolines when aminobenzyl alcohols were used as alkylating agents. In this way, different 3-keto quinolines can be shortly prepared in acid or base-free conditions in good yields under microwave dielectric heating. It is worthy to note that this procedure constitutes an example of high atom efficiency reaction and, to our knowledge, it is the first example of a Ru catalysed Friedländer quinoline synthesis heating under microwaves.

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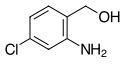
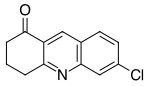
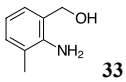
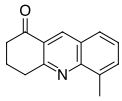
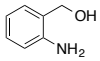
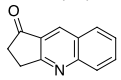
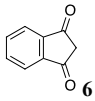
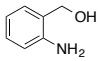
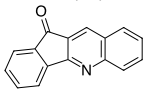
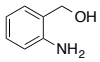
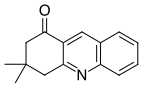
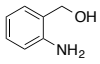
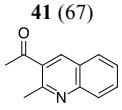
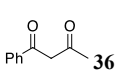
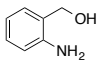
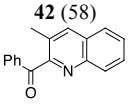
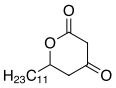
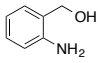
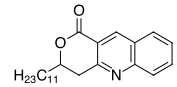
Table 3 Scope of quinoline syntyhesis

Entry	Dicarbonyl compound	Alcohol	Product (yield, %)
1	 **10**	 **32**	 **37** (70)
2	 **10**	 **33**	 **38** (62)
3	 **11**	 **30**	 **39** (49)
4	 **6**	 **30**	 **40** (61)
5	 **34**	 **30**	 **41** (67)
6	 **35**	 **30**	 **42** (58)
7	 **36**	 **30**	 **43** (52)
8	 **1**	 **30**	 **44** (44)

Experimental

2-(3-Phenylpropyl)-1,3-indandione (8), general procedure.

In a glass vial containing a magnetic stirring bar, 1,3-indandione **6** (100 mg, 0.68 mmol) was dissolved in 1 mL of toluene under nitrogen. 3-Phenyl-1-propanol **7** (93 mg, 93 µL, 0.68 mmol), Hantzsch ester (17 mg, 0,068 mmol) and [$Ru(CO)(PPh_3)_3HCl$] (26 mg, 0,027 mmol) were added and the vial sealed. The mixture was stirred in a sand bath heated at 160 °C for 16 h. Then, the mixture was cooled to room temperature, and the reaction was checked by TLC (petroleum ether/EtOAc, 7:3). The solvent was removed under *vacuum* and the crude reaction mixture was loaded directly onto a column for flash chromatographic purification (eluent: from petroleum ether to

petroleum ether/EtOAc, 7:3) which gave pure **8** (105 mg, 58%) as a yellowish waxy material. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.88 (m, 2H), 7.84 – 7.75 (m, 2H), 7.22 (t, *J* = 7.0 Hz, 2H), 7.12 (d, *J* = 7.5 Hz, 3H), 3.00 (t, *J* = 6.0 Hz, 1H), 2.59 (d, *J* = 7.7 Hz, 2H), 1.98 (d, *J* = 9.8 Hz, 2H), 1.71 (t, *J* = 7.9 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 204.4, 146.0, 145.2, 131.9, 129.4, 126.7, 81.0, 80.7, 80.4, 56.9, 39.5, 31.8. GC/MS: R_t 22.86 min; m/z 264 ($C_{18}H_{16}O_2$). HRMS (EI): Calcd for $C_{18}H_{16}O_2Na$ $[M+Na]^+$: 287.1048, found 287.1047

3,4-Dihydro-2H-acridin-1-one (31), general procedure

A 10-mL vial for MW equipped with a magnetic stirring bar was charged with 1,3-cyclohexanedione (100 mg, 0.89 mmol) under nitrogen. Dry toluene (1 mL), 2-aminobenzyl alcohol (110 mg, 0.89 mmol), $[Ru(CO)(PPH_3)_3HCl]$ (34 mg, 0.036 mmol) and 25 μL of ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate were added and the mixture was stirred under MW dielectric heating for 30 min at 120 °C (max internal pressure 180 psi). Then, the mixture was cooled to room temperature, and the reaction was checked by TLC (petroleum ether/EtOAc, 7:3). The solvent was removed under *vacuum* and crude reaction mixture was loaded directly onto a column for flash chromatographic eluted with a gradient of petroleum ether to petroleum ether/EtOAc, 7:3. Pure **31** (127 mg, 73%) was a yellowish solid. M.p. 108-109 °C (lit m.p. 109-110 °C)[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 3.20 (t, *J* = 6.1 Hz, 2H), 2.73 – 2.58 (m, 2H), 2.16 (p, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 161.5, 149.2, 136.6, 131.8, 129.2, 128.1, 126.3, 126.2, 125.8, 38.6, 33.0, 21.3. HRMS (EI): Calcd for $C_{13}H_{12}NO$ $[M+H]^+$ 198.0919, found 198.0921.

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Notes and references

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Mono alkylation of 1,3-dicarbonyls is now possible with alcohols and catalytic amount of Hantzsch ester under Ru catalysis.