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Environmentally benign nucleophilic substitution reaction of arylalkyl halides in water using CTAB as the inverse phase transfer catalyst†

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An environmentally benign, practically scalable and highly selective *C*-arylalkylation of active methylene compounds is developed using CTAB as the inverse phase transfer catalyst in water. The methodology developed is elaborated into the one-pot synthesis of quinoline derivatives and also applicable to the regioselective *N*-aralkyl of 2-pyridones.

The alkylation of 1,3-dicarbonyl compounds and other active methylene compounds is a fundamental and useful transformation involving C–C bond formation.[1] This reaction is generally accomplished by treating various metal enolates with alkylating reagents such as alkyl halides or alkyl sulfonates. These reactions warrant the use of polar aprotic solvents such as DMF/DMSO as the reaction medium and the use of appropriate strong bases, *viz.* sodium hydride and *t*-BuOK, in most cases.[2] Direct nucleophilic substitution of the hydroxy group in alcohols with enolate nucleophiles was achieved by various methods involving either a high reaction temperature or use of Lewis[3a] and heteropoly acids[3b,c] as the catalytic promoter or by employing transition metal reagents.[4] The majority of these approaches are largely limited to laboratory scale synthesis and are highly substrate dependent.[5] Hence, development of an environmentally benign process for this fundamental C–C bond formation might be beneficial when applied on the industrial scale. Owing to the increased awareness of the need for sustainable technology that complies with Green chemistry principles, chemists worldwide have resorted to safer, environmentally benign practices that avoid the formation of waste at the locus.[6] Studies indicate that over 80% of organic waste generated from both academic and industrial set-ups is attributed to the use of solvents as the reaction medium.[7] The use of solvents in organic synthesis has become indispensable as most substrates and catalysts are soluble only in organic solvents. Stringent environmental concerns have resulted in the shift in the paradigm, driving scientists across the globe to resort to greener solvents as well as various alternate reaction media such as ionic liquids[8a] and supercritical CO_2.[8b] On the other hand, water, the universal solvent in which most biochemical transformations occur in living systems, has been conveniently ignored when planning a synthetic strategy; or more often than not its use is limited to that of a co-solvent or as an additive. This selective exclusion of water is attributed to the poor solubility of organic substrates/reactants and catalysts in water.

To address the solubility issues, chemists have resorted to the use of surfactants.[9] Due to the hydrophobic effects involved, they form a cage around the organic substrates wherein the reaction takes place.[10] In a more similar manner, use of inverse phase transfer catalysts transports two immiscible reactants into the aqueous phase and the reaction proceeds.[11] This concept was successfully invoked by Shimizu and co-workers in their study of base mediated alkylation of active methylene compounds with various alkyl halides using the water-soluble calix[*n*]arenes (n = 4, 6 and 8) as an inverse phase-transfer catalysts (i-PTC) that contains trimethylammoniomethyl groups on the upper rim.[12] Inspired by this work, we envisaged that regioselective, mono-*C*-aralkyl/alkylation can be effected with equal efficiency using various surfactants that are commercially available and economically viable on an industrial scale. In this regard, herein, we report an environmentally benign, relatively milder and practical approach for regioselective *C*-aralkylation of 1,3-dicarbonyl derivatives that employs CTAB as the i-PTC and enables us to utilize water as the reaction medium. The application of the methodology can be extended to the multi-gram scale synthesis of various industrially useful key API starting materials and intermediates.

Our initial efforts were directed towards identifying an appropriate catalyst for *C*-benzylation of β-ketoester **1a**. Accordingly, commercially available non-ionic surfactants such as Tween 40™, TPGS-750-M™, Triton X-100™ and Brij 58™ were screened initially with limited or no desired reaction using K_2CO_3 as the base.

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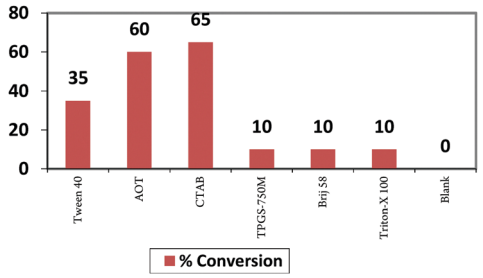
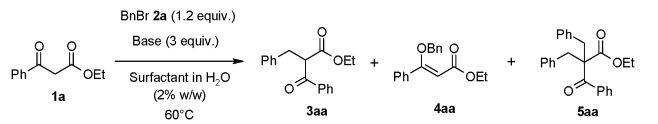


Fig. 1 Influence of various surfactants/i-PTC catalysts on *C*-benzylation of ethyl-3-oxo-3-phenylpropanoate using K_2CO_3 as the base at 60 °C.

However, switching from non-ionic surfactants to ionic surfactants such as AOT™ and CTAB had a dramatic effect on the reaction profile, rendering mono *C*-benzylated product **3aa** in respectable yield (Fig. 1). Details of the same are incorporated in the ESI.†

Screening of various bases was taken up next. Accordingly, various bases were screened using CTAB in H_2O at 60 °C. The progress of the reaction was monitored using LCMS and the results are summarized in Table 1. Use of milder bases such as $NaHCO_3$ and K_3PO_4 resulted in incomplete consumption of starting β-ketoester **1a** after 16 h, with moderate conversion to the desired product **3aa** along with a small amount of undesired reaction (Table 1, entries 1 and 2). Switching from inorganic to organic bases was not effective as well, as the use of DIPEA resulted in formation of a mixture of *C*- and *O*-benzylated products (Table 1, entry 3), whereas use of Et_3N resulted in partial conversion (Table 1, entry 4). DABCO was inefficient in effecting the conversion and DBU resulted in the formation of a complex reaction profile (Table 1, entries 5 and 6). The best result was obtained when K_2CO_3 was used as the base (Table 1, entry 7). On the contrary, increased basicity resulted in formation of a mixture of mono- and poly alkylated products as observed with the use of Cs_2CO_3, NaOH and CsOH as the base

Table 1 Screening of bases for *C*-benzylation of ethyl-3-oxo-3-phenylpropanoate using CTAB in water



		% conversion by LCMS[a]			
Entry	Base	**1a**	**3aa**	**4aa**	**5aa**
1	$NaHCO_3$	36	55	3	0.9
2	K_3PO_4	18	53	6	6
3	DIPEA	6	68	10	4
4	Et_3N	22	42	1.2	0.5
5	DABCO	53	6	0.2	0.5
6[b]	DBU	0	32	2	10
7	**K_2CO_3**	**8**	**80**	**5**	**2**
8	Cs_2CO_3	12	63	10	6
9	NaOH	0	46	3	27
10	CsOH	0	43	2	32

[a] In all the cases the ratio was monitored using LCMS analysis of the crude reaction mixture. [b] Formation of an unidentified product was observed at *ca.* 35%.

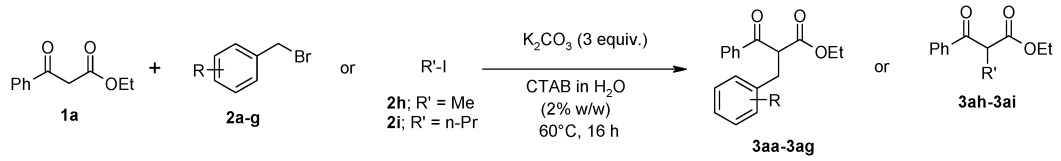
in entries 8–10. With optimized conditions in hand, the scope of various differentially substituted benzyl halides and other alkyl halides was studied next.

Table 2 outlines the scope of the various electrophiles employed. It was observed that substitution on the benzyl halides does not have any detrimental effect on the outcome of the reaction, as both electron releasing (Table 2, entries 1–4 and entries 6 and 7) and electron withdrawing substituents (Table 2, entry 5) were found to deliver the desired mono-alkylated products **3aa–3ag** in high yields. Also, alkyl halides, *viz.* methyl iodide (**2h**) and *n*-propyl iodide (**2i**), were employed in these conditions quite effectively rendering the mono-*C*-alkylated product **3ah** and **3ai**, respectively, in good yields (Table 2, entries 8 and 9). In all these trials, very little side reactions (<10%) were observed as deduced by the LCMS analysis of the crude reaction mixture. The scope of the nucleophiles was studied by choosing diethyl malonate (**1b**) as the benchmark substrate. Thus, **1b** was subjected to selective *C*-aralkylation with various differentially substituted benzyl bromide derivatives **2a–2g** to furnish the desired mono-*C*-benzylated malonate derivatives **3ba–3bg** in an uneventful manner as shown in Table 3, entries 1–7. After successfully studying the substrate scope of the methodology, it was envisaged that the same methodology can be employed for the synthesis of quinoline derivatives in 'one-pot' using water as the reaction medium.

Quinoline motifs are part of the structure of various natural products and were found to exhibit various biological activity functioning as antiviral, antimalarial and antituberculosis agents.[13] Conventional strategies often require harsh reaction conditions and are often marred by unwanted side reactions.[14] Condensation of *o*-aminobenzaldehdyes with ketones (the Friedlander approach) is another useful strategy, however, the stability and economic viability of the key SM demerits the approach.[15] Transition metal catalyzed reactions of *o*-haloanilines with allyl alcohol equivalents[16] are widely used among various other useful alternates.[17,18] Recently, Xing *et al.* reported the reductive cyclization of *o*-nitrochalcones to furnish quinolines.[19] Based on which, we reasoned that the *C*-benzylation of 1,3-dicarbonyl compounds with *o*-nitro benzyl-bromide (**2j**) and subsequent reductive cyclization in "one-pot" would lead to the formation of 2,3-disubstituted quinoline derivatives. To test the hypothesis, as depicted in Scheme 1, ethylbenzoyl acetate (**1a**) was reacted with *o*-nitrobenzyl bromide (**2j**) using the optimized protocol to procure the benzylated ketoester **3aj**. Upon completion of the reaction, Zn/NH_4Cl, as performed by Lipshutz *et al.*,[20] was introduced into the reaction medium leading to the reductive cyclization of *in situ* generated aniline **6aj**, to furnish **7aj**. **7aj** underwent oxidative aromatization, rendering 2,3-disubstituted quinoline derivative **9aj**, in a tandem fashion with good overall yield.

With successful demonstration of the methodology for the quinoline synthesis, we then turned our attention towards the regioselective *N*-alkylation of 2-pyridones. The ambident character of 2-pyridones makes selective *N- versus O*-alkylation a formidable problem[21] and to date it remains an actively pursued research area.[22,23] In this context, we attempted the *N*-benzylation of 2-1*H*-pyridone (**10**) using various bases with 2% w/w of CTAB in water. The study revealed K_2CO_3 to be the base of choice and

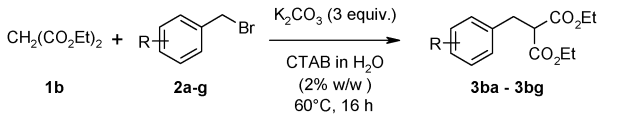
Table 2 *C*-Arylalkylation of ethyl-3-xxo-3-phenylpropanoate using K_2CO_3 and CTAB in water: scope of electrophiles



Entry	Halides	R/R′	Product distribution by IPC-LCMS 1a	3	4	5	Product	Yield[a] (%)
1	**2a**	H	8	80	5	2	**3aa**	65 (60)[b]
2	**2b**	4-Cl	2.8	70	7	5	**3ab**	57
3	**2c**	4-I	7	77	0.9	6	**3ac**	63
4	**2d**	4-Me	5	82	n.d.	4.5	**3ad**	69 (30)[b]
5	**2e**	4-NO_2	15	73	n.d.	n.d.	**3ae**	61[b]
6	**2f**	4-Br	Trace	80	3	8	**3af**	71
7[c]	**2g**	4-OMe	4	60	4	3	**3ag**	65
8	**2h**	Me	NA	NA	NA	NA	**3ah**	60
9	**2i**	n-Pr	NA	NA	NA	NA	**3ai**	70

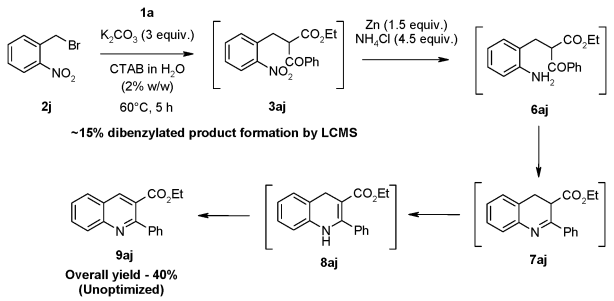
[a] Isolated yield after column purification. [b] Isolated yield obtained using AOT. [c] 25% of the corresponding acid of **3ag** was found in LCMS analysis. Note: all reactions were carried out on a 1 g scale of **1a** and were analysed by IPC-LCMS after 16 h, entry 5 in 4 h. Entries 8 and 9 were monitored by TLC. Legend: NA – Data not available; n.d. – not detected. Extractions were necessary in these cases owing the physical nature of the product and are relative to the scale of the reaction. Solvent extractions can be conveniently avoided when performed on a larger scale.

Table 3 *C*-Arylalkylation of diethylmalonate (**1b**) using K_2CO_3 and CTAB in water: scope of electrophiles



Entry	Halides	Product	Yield[a] (%)
1	**2a**	**3ba**	65
2	**2b**	**3bb**	59
3	**2c**	**3bc**	55[b]
4	**2d**	**3bd**	60[b]
5	**2e**	**3be**	30[c]
6	**2f**	**3bf**	58
7	**2g**	**3bg**	62

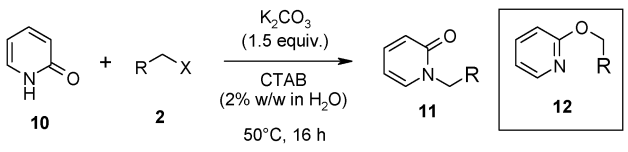
[a] Isolated yield after column purification. [b] 15% v/v THF was added as the co-solvent. [c] Isolated yield obtained using AOT as a surfactant, as no desired reaction was observed using CTAB. Note: all reactions were carried out on a 1 g scale of **1b** for 16 h and the progress of the reaction was monitored by TLC.



Scheme 1 Indirect Friedlander's approach: "one-pot" synthesis of quinolines using water as the reaction medium and the mechanistic pathway.

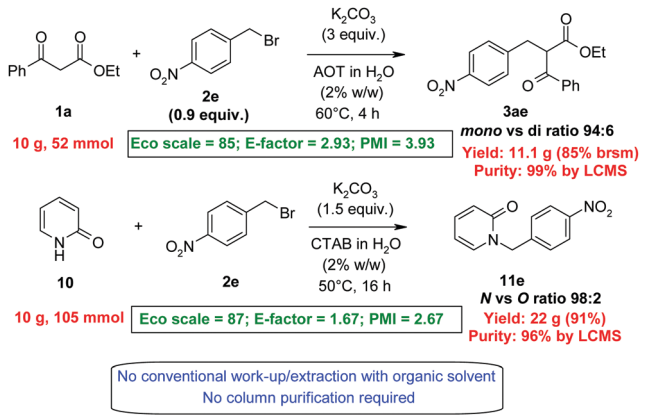
LCMS analysis of the crude reaction mixture, after 3 h, revealed the formation of *N*-benzylated pyridone **11a** in a highly regioselective manner with only traces of 2-benzyloxy pyridine (**12a**) being formed (Table 4, entry 1). When benzyl chloride was employed, the reaction was equally efficient albeit with prolonged reaction time (~24 h). With the optimized conditions in hand, attention was turned towards studying the substrate scope of the reaction. Accordingly, various *para*-substituted benzyl bromides were efficiently coupled with pyridone **10** to furnish their respective

Table 4 Scope of *N*-arylalkylation of 2-pyridones using K_2CO_3 and CTAB in water



Entry	RCH_2Br		N *vs.* O[a] **11 : 12**		Yield of **11** (%)
1	$PhCH_2Br$	**2a**	99 : 1	**11a**	82
2	$PhCH_2Cl$	**2a′**	87 : 13	**11a**	—
3	4-Cl-C_6H_4-CH_2Br	**2b**	96 : 4	**11b**	76
4	4-I-C_6H_4-CH_2Br	**2c**	93 : 7	**11c**	86
5	4-Me-C_6H_4-CH_2Br	**2d**	97 : 3	**11d**	86
6	4-NO_2-C_6H_4-CH_2Br	**2e**	93 : 2	**11e**	75
7	4-Br-C_6H_4-CH_2Br	**2f**	92 : 8	**11f**	85
8	2-NO_2-C_6H_4-CH_2Br	**2j**	98 : 2	**11j**	75
9	3-Cl-C_6H_4-CH_2Br	**2k**	90 : 10	**11k**	70
10	3-NO_2-C_6H_4-CH_2Br	**2l**	98 : 2	**11l**	70
11	2,4,6-$(Me)_3$-$C_6H_2CH_2Br$	**2p**	13 : 1[c]	**11p**	63
12	$PhCOCH_2Br$	**2q**	≥19 : 1[c]	**11q**	72
13	CH_2=CH-CH_2Br	**2r**	≥19 : 1[c]	**11r**	62 (87)[d]
14	$CH_3(CH_2)_3CH_2I$	**2s**	≥19 : 1[c]	**11s**	69
15	i-Pr-I	**2t**	Trace product		

[a] In all the cases the ratio was monitored using LCMS analysis of the crude reaction mixture, unless or otherwise stated. [b] Isolated yield after column purification. [c] Ratio was monitored using ^{1}H NMR analysis of the crude reaction mixture. [d] Yield based on the unreacted **10**.



Scheme 2 Application of the methodology on a larger scale.

N-benzylated pyridones **11b–f** as depicted in Table 4, entries 3–7. The use of *o*- or *m*-substituted benzyl bromides, **2j–p**, as the electrophile does not have any detrimental effect on the reaction outcome, thus rendering the pyridone derivatives **11j–p** with good yields and high regioselectivity (Table 4, entries 8–11). The regioselective formation of the *N*-benzylated pyridone was further ascertained based on the observation of cross peaks in the NOESY spectra performed on pyridone **11e**.[24] Further, the scope was enhanced by using various alkyl halides. Thus, phenacyl bromide (**2q**), allyl bromide (**2r**) and 1-iodopentane (**2s**) provided the desired *N*-alkylated pyridone **11q**, **11r** and **11s**, respectively (Table 4, entries 12–14), whereas isopropyl iodide (**2t**) was found to be very sluggish to react and the desired product was formed in a trace amount (Table 4, entry 15).

Finally, the methodology developed was probed for its application on a large scale and for evaluating its "*greenness*" (Scheme 2). Thus, 4-nitrobenzyl bromide (**2e**) was chosen as a representative substrate and was subjected to the arylalkylation reaction with ethyl-3-oxo-3-phenylpropanoate (**1a**) using the optimized conditions on a 10 g (52 mmol) scale. Upon completion, the reaction mixture was allowed to stand at rt and the organic layer was separated and stirred with water at 50 °C and further digested with hexanes to procure the desired product **3ae** with 99% purity by LCMS. The environmental impact of this reaction condition, measured using the reported modules,[25] revealed an EcoScale value of 85 and an *E*-factor of 2.93, suggesting that the reaction conditions are process friendly as well as environmentally friendly in nature.

In a similar manner, bromide **2e** was treated with 2-pyridone 10 (10 g, 105 mmol) to furnish the desired *N*-benzylated pyridone **11e** with high regioselectivity and excellent yield. Conventional work-up was avoided by further diluting the reaction mixture with ice-cold water, thus leading to the precipitation of the desired product **11e** as an off-white solid with 96% purity by LCMS. Measurement of the "*green metrics*" for the reaction suggests this to be an excellent synthesis with an EcoScale value of 87 and an *E*-factor of 1.67.

Conclusions

In summary, a highly regioselective mono-*C*-arylalkylation of active methylene compounds using CTAB as the inverse phase transfer catalyst employing water as the reaction medium is developed and demonstrated in a multi-gram scale synthesis of various mono-benzylated malonate and benzoylacetate derivatives with good isolated yield. The utility of the protocol was further exemplified in the "one-pot" indirect Friedlander's synthesis of quinolines and highly *N*-selective benzylation of pyridones. Further, the methodology was studied for its large scale application and the measure of the "green metrics" suggested the methodology to be environment as well as process friendly. The physical chemistry/mechanistic aspects of the methodology are being probed so as to adopt the same in a highly efficient manner on an industrial scale in the synthesis of APIs and other important feedstock starting materials.

Author contributions

The overall research program was managed by GS. Conceptualization of the project and the management of research activity were done by SAM, AKG and AVG. *C*-Benzylation reactions were performed by AKG, TJ, AV and PB under the supervision of AVG. Quinoline synthesis and pyridone *N*-alkylation were performed by NAV and VK under the supervision of SAM. SAM wrote the overall story of the manuscript along with AVG. The manuscript was further edited by AKG and GS. All the authors discussed the manuscript.

Conflicts of interest

The authors declare no competing financial interest.

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