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ARTICLE TYPE

Transition metal-free synthesis of α-ketoamides from arylmethyl ketones and alkylphosphoramides

Ahalya Behera, Wajid Ali, Manisha Tripathy, Diptimayee Sahoo and Bhisma K. Patel*

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A transition metal-free protocol has been developed for the synthesis of α-ketoamides from aryl methyl ketones and alkylphosphoramides in the presence of oxidant, aqueous *tert*-butyl hydroperoxide (TBHP). A series of aryl methyl ketones having both electron-donating as well as electron-withdrawing groups were successfully employed for the synthesis of their corresponding α-ketoamides using hexamethylphosphoramide and other alkylphosphoramides.
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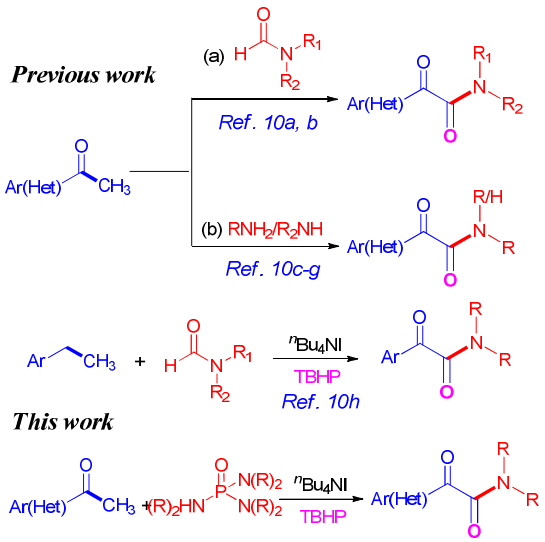
Introduction

Cross-dehydrogenative coupling (CDC) has contributed tremendously in the development of atom and step-economic process for the synthesis of complex molecular architectures from simple precursors. The CDC process plays a pivotal role in bringing about the transformation of C–H bonds of all types (sp, sp^2 and sp^3) to C–C and C–heteroatom bonds.[1] Of various C–heteroatom bonds, the construction of C–N bond is one of the most fundamental challenge in the synthesis of biologically important molecules, natural products, pharmaceuticals and other functional materials.[2] Among diverse C–N bond forming reactions, synthesis of α-ketoamide via C–N bond formation is one of the important reaction, as it constitutes the basic subunits of many vital molecules. These motifs are used in the designing of peptidase inhibitors,[3a] histone deacetylases[3b] and human cytosolic phospholipase A_2,[3c,d] which is applicable for inhibiting several classes of proteases such as serine, cysteine and HIV.[3e-g] Because of the wide applicability of α-ketoamides, a number of synthetic routes have been developed for their synthesis.[4-8]

Arylmethylketone can be converted into phenylglyoxal in the presence of an appropriate oxidant that may serve as a α-ketyl (ArCOCO-) surrogate.[9] This α-ketyl group may couple with the *in situ* generated amines from phosphoramides under an oxidative condition to afford a α-ketoamide. Keeping this in mind, when acetophenone (**a**) (0.5 mmol) was treated with hexamethylphosphoramide (HMPA) (**1**) (1.5 mmol) in the presence of *tetra*-butylammonium iodide ($^nBu_4NI$) (20 mol%), chlorobenzene (PhCl) (2 mL) and a decane solution of *tert*-butylhydroperoxide (TBHP) (4 equiv.) at 130 °C, formation of *N,N*-dimethyl-2-oxo-2-phenylacetamide (**1a**) was observed in 61% isolated yield. Previously, arylmethylketones have been employed for the synthesis of α-ketoamide by coupling it with dialkylformamides and primary/secondary amines.[10a-g] Similarly α-ketoamidehave have also been synthesised from ethylarenes and dialkylformamide under a metal free condition.[10h] However, synthesis of α-ketoamides using arylmethylketones as the α-ketoaryl (ArCOCO-) equivalents and alkylphosphoramides as the amine source has not been reported so far (Scheme 1). Invariably, hexamethylphosphoramide is used as a solvent in organic reactions, but its use as the source of amine for the synthesis of α-ketoamide is explored for the first time.



Scheme 1 Synthesis α-ketoamides from arylmethylketones and ethylarenes.

Results and discussion

Department of Chemistry, Indian Institute of Technology Guwahati, 781 039, Assam, India. Fax no. +91-3612690762; E-mail: patel@iitg.ernet.in

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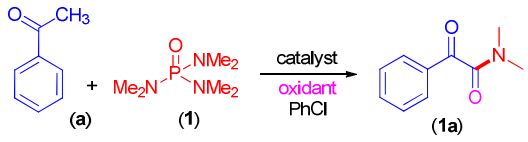
To further improve the yield of the coupled product (**1a**) obtained from arylmethylketone (**a**) and hexamethylphosphoramide (**1**), various reaction parameters were scrutinized. Initially, a variety of oxidants such as aq. TBHP (66%), DTBP (36%), 30% aq. H_2O_2 (00%), $K_2S_2O_8$ (27%) and $(PhCOO)_2O$ (BPO) (15%), were tested (Table 1, entries 2–6), from which aq. TBHP was found to be the ideal (Table 1, entry 2). The use of other halogen analogues such as TBAB, I_2 and KI, in lieu of TBAI were found to be far less effective (Table 1, entries 7–9). An increased amount of catalyst loading (30 mol%) was not so much beneficial (Table 1, entry 10), nevertheless a higher loading of oxidant to 6 equiv. improve the product yield by another 6% (Table 1, entry 11). Further, increase in the oxidant loading to 8 equiv., did not show any significant improvement in the product yield (Table 1, entry 12). To further improve the yield of the product (**1a**), various solvents viz. 1,2-dichloroethane (DCE), CH_3CN and EtOAc were screened (Table 1, entries 13–15) but all were found to be inferior in comparision to PhCl (Table 1, entry 11). Next, the effect of reaction temperature on the product formation was examined and it was found that the reaction carried out both at higher (145°C) and lower (110 °C) temperature had adversely affected the product (**1a**) yield (Table 1, entries 16 and 17). Under otherwise identical conditions either in the absence of TBAI or TBHP failed to give the desired product (Table 1, entries 18 and 19) suggesting the vital role of both, in achieving the above transformation.

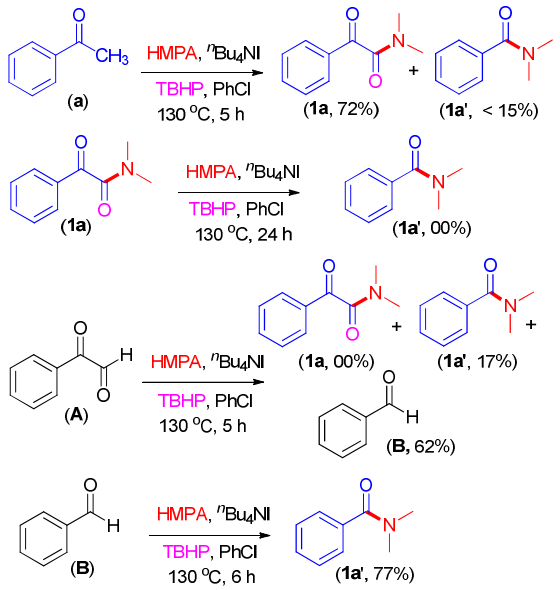
Table 1 Screening of the reaction conditions[a,b]



Entry	Catalyst (mol%)	Oxidant (equiv.)	Solvent	Temp (°C)	Yield (%)
1	TBAI (20)	TBHP (4)	PhCl	130	61[c]
2	TBAI (20)	TBHP (4)	PhCl	130	66[d]
3	TBAI (20)	DTBP (4)	PhCl	130	36
4	TBAI (20)	H_2O_2 (4)	PhCl	130	00
5	TBAI (20)	$K_2S_2O_8$ (4)	PhCl	130	27
6	TBAI (20)	BPO (4)	PhCl	130	15
7	TBAB	TBHP(4)	PhCl	130	52
8	I_2 (20)	TBHP (4)	PhCl	130	47[d]
9	KI (20)	TBHP (4)	PhCl	130	12[d]
10	TBAI (30)	TBHP (4)	PhCl	130	67[d]
11	**TBAI (20)**	**TBHP (6)**	**PhCl**	**130**	**72[d]**
12	TBAI (20)	TBHP (8)	PhCl	130	73[d]
13	TBAI (20)	TBHP (6)	DCE	130	54[d]
14	TBAI (20)	TBHP (6)	CH_3CN	130	63[d]
15	TBAI (20)	TBHP (6)	EtOAc	130	65[d]
16	TBAI (20)	TBHP (4)	PhCl	145	62[d]
17	TBAI (20)	TBHP (4)	PhCl	110	50[d]
18	-	TBHP (4)	PhCl	130	00[d]
19	TBAI (20)	-	PhCl	130	00

[a]Reaction conditions: acetophenone (**a**) (0.5 mmol), catalyst, HMPA (1.5 mmol), solvent (2 mL), oxidant. [b]Yields of isolated pure product. [c]decane solution of TBHP, [d]aq. TBHP (70 wt% in water).

During the course of optimisation, it was observed that the duration of reaction play a significant role on the product yield. When the reaction was heated beyond 45 minutes, in addition to the formation of α-ketoamide (**1a**), appearance of another product in <15% having R_f lower than the α-ketoamide was also noticed. Spectroscopic analysis of the product reveals its structure to be an amide (**1a′**) (Scheme 2). Now a query arises whether product (**1a′**) is formed via the decomposition of α-ketoamide (**1a**) or via the coupling of benzaldehyde (obtained from the decomposition of phenylglyoxal) and the dimethylamine (generated by the decomposition of HMPA)? To check this, when a pre-synthesised α-ketoamide (**1a**) was subjected to the present reaction condition, formation of an amide (**1a′**) was not observed even after 24 h (Scheme 2). Again, when phenylglyoxal (**A**) was taken in lieu of acetophenone (**a**) under otherwise identical condition, formation of amide (**1a′**) along with the formation of benzaldehyde (**B**) was observed. This observation confirms the formation of phenylglyoxal in small amount from acetophenone, which results in the formation of amide (**1a′**) in the reaction. A similar reaction with benzaldehyde in lieu of phenylglyoxal gave exclusively *N*,*N*-dimethyl benzamide (**1a'**) in 77% yield. This confirms the *in situ* generation of benzaldehyde in the reaction medium. Finally, the optimised condition for this transformation is the use of acetophenone (0.5 mmol), hexamethylphosphoramide (1.5 mmol), $^nBu_4NI$ (20 mol%), chlorobenzene (2 mL) and aq. TBHP (70 wt% in H_2O) (3 mmol) at 130 °C for 45 minutes (Table 1, entry 11).



Scheme 2 Control experiments for the formation of amide.

With this optimised condition in hand, different arylmethylketones (**a**–**l**) bearing both electron-donating and electron-withdrawing groups were subjected to the current reaction condition with hexamethylphosphoramide (**1**). As can be seen from Scheme 3, the presence of substituents on the aryl ring of arylmethylketone play a significant role on the yields of *N*,*N*-dimethyl-2-oxo-2-phenylacetamides. Arylmethylketones substituted with electron-donating group like –Me (**b**) gave its corresponding α-ketoamide (**1b**) in 78% yield. On the other hand, the presence of moderately electron-withdrawing groups such as –I (**c**), –Br (**d**), –Cl (**e**) and –F (**f**) in the arylmethylketone reduced the product (**1c**–**1f**) yields ranging between 70–54% (Scheme 3) compared to their electron-neutral analogue. Further reduction in the product (**1g**) yield (48%) was observed when a strongly electron-withdrawing group like –

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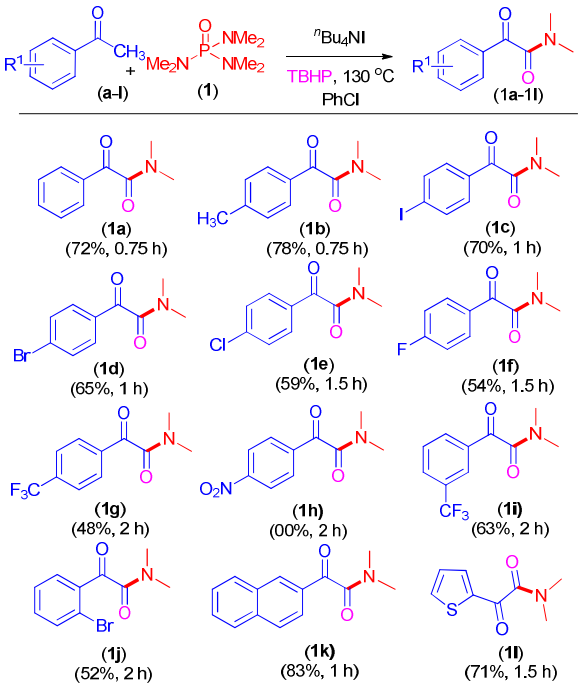
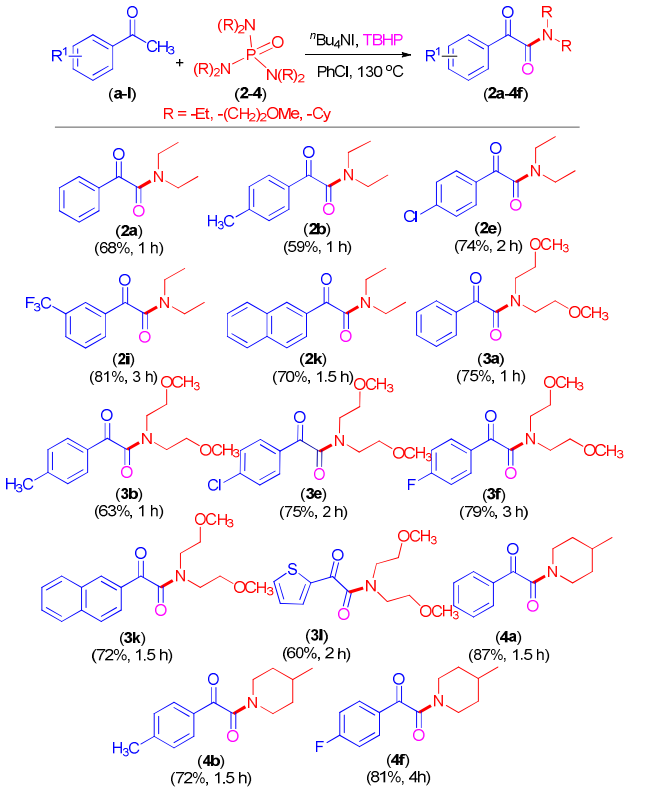
CF_3 (**g**) is present at the *para* position of arylmethylketone (**g**). When the electron-withdrawing power of the substituent is increased further, as in *p*-nitroacetopheneone (**h**), a complete failure of the reaction was noticed. However, when the $–CF_3$ group was moved to the *meta* position (**i**), its electronic effect was not such prominent to that when it is present at the *para* position giving product (**1i**) in decent yield (63%). When a moderately electron-withdrawing group such as –Br is present at the *ortho* position of arylmethylketone (**j**) further reduction in the yield was observed which may be due to both electronic as well as steric reasons. Other than these, an excellent yield of *N*,*N*-dimethyl-2-naphthamide (**1k**) was obtained from 2-acetonaphthone (**k**). A good yield of the α-ketoamide (**1l**) formation was also observed when 2-acetylthiophene (**l**) was used in the reaction process.



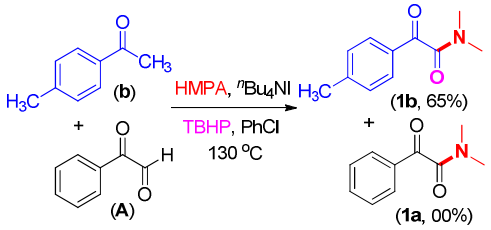
Scheme 3 Substrate scope for the formation of *N*,*N*–dimethyl aromatic *α*-ketoamide[a,b]. [a]Reaction conditions: arylmethylketones (**a–l**) (0.5 mmol), HMPA (**1**) (1.5 mmol), tetrabutylammonium iodide (^{n}Bu$_4$NI) (20 mol%), chlorobenzene (2 mL), TBHP (70 wt% in H_2O) (6 equiv.), time (45 mins–2 h) at 130 °C. [b]Yields of isolated pure product.

Adopting our previous optimised condition, a library of α-ketoamides were also synthesised using different arylmethylketones (**a–l**) and hexalkylphosphoramides (**2–4**) as shown in Scheme 4. Acetophenone substituted with an electron--donating group like 4′-methylacetophenone (**b**) gave lesser yield of α-ketoamide (**2b**) compared to the un-substituted one (**2a**) when coupled with hexaethylphosphoramide (**2**). On the other hand, presence of electron-withdrawing groups like 4′-Cl (**e**) and 3′-CF_3 (**i**) enhance the reactivity of arylmethylketones, providing their corresponding α-ketoamides (**2e** and **2i**) in 74% and 81% yields respectively. 2′-Acetonaphthone (**k**) was also successfully employed as a good ketoaryl source for the synthesis of α-ketoamide giving product (**2k**) in 70% yield. Hexa(methoxyethyl)phosphoramide (**3**) was successfully used as the amine source for the formation of different *N*,*N*-bis(methoxyethyl) substituted phenylacetamides (**3a**, **3b**, **3e**, **3f**, **3k** and **3l**). Cyclic amine based phosphoramides were also utilised as the amine source similar to acyclic phosphoramides. Tri(4-methylpiperidine)phosphoramide (**4**) reacted with electron-neutral (**a**), electron-donating 4′-Me (**b**) as well as electron-withdrawing 4′-F (**f**) acetophenones gave their respective α-ketoamide (**4a**, 87%), (**4b**, 72%) and (**4f**, 81%) in good yields (Scheme 4).



Scheme 4 Substrate scope for the formation of *N*,*N*-disubstituted α–ketoamides[a,b]. [a]Reaction conditions: acetophenone (**a**) (0.5 mmol), phosphoric acid triamide (**2-4**) (1.5 mmol), tetrabutylammoniun iodide (^{n}Bu$_4$NI) (20 mol%), TBHP (70 wt% in H_2O) (6 equiv.), time (1–4 h) at 130 °C .[b]Yields of isolated pure product.

Previously, it is known that acetophenone in the presence of a suitable oxidant such as SeO_2 is transformed to a phenylglyoxal.[11] Therefore; we envisaged that in the presence of an oxidant such as TBHP instead of SeO_2, acetophenone may be converted to phenylglyoxal in the reaction medium. To ascertain the exact reaction intermediate when a reaction was performed with an equimolar mixture of phenylglyoxal (**A**) and 4′-methylacetophenone (**b**) under an otherwise identical condition. Isolation of the only product *N*,*N*-dimethyl-2-oxo-2-(*p*-tolyl)acetamide (**1b**) (derived from the coupling of 4′-methylacetophenone (**b**) and the *in situ* generated dimethylamine from HMPA) in 65% yield suggests that the phenylglyoxal is not the active intermediate in the reaction (Scheme 5). This observation is consistent with the observation in Scheme 2.



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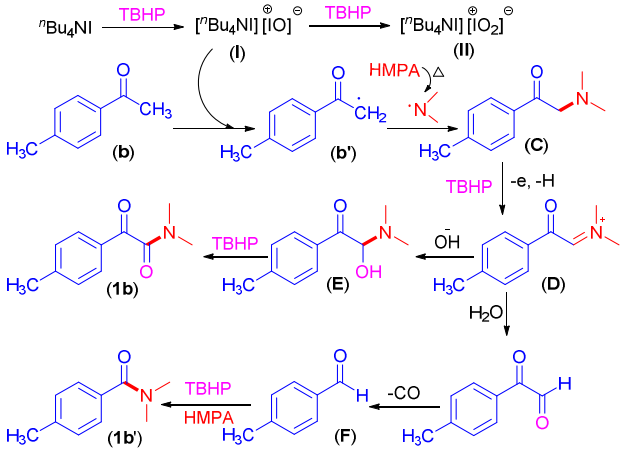
Scheme 5 Cross-over experiment between 4′-methylacetophenone (**b**) and phenylglyoxal.

By summing up all the above experimental results and from the literature precedence,[1i,10] a plausible mechanism is proposed for the formation α-ketoamide (Scheme 6). Initially, from "^{n}Bu$_4$NI-TBHP" combination, the active iodine species ammonium hypoiodite ([^{n}Bu$_4$N]$^+$[IO]$^-$) (**I**) or iodite ([^{n}Bu$_4$N]$^+$[IO$_2$]$^-$) (**II**) is generated.[10m,13] The formation of hypervalent iodine species ([^{n}Bu$_4$N]$^+$[IO]$^-$) (**I**) and ([^{n}Bu$_4$N]$^+$[IO$_2$]$^-$) (**II**) have been confirmed by the detection of [IO]$^-$ and [IO$_2$]$^-$ from the ESI mass analysis of the reaction mixture (see SI).[1i,10m] The hypervalent iodine species (**I**) or (**II**) then abstracts a hydrogen atom from the aryl methyl ketone to generate a α-keto methyl radical (**b′**). This radical species (**b′**) couples subsequently with the dimethylaminyl radical (generated from the thermal decomposition of HMPA) to give the intermediate (**C**). Another intermediate (**D**) is generated from intermediate (**C**) via a one electron oxidation. HRMS analysis of the reaction mixture confirmed the intermediacy of both (**C**) and (**D**) (See SI). Then nucleophilic attack of a hydroxide ion to the intermediate (**D**) produce a keto-hydroxy intermediate (**E**), which is finally oxidised to the desired α-ketoamide (**1b**) in the presence of TBHP. This mechanism also accounts for the formation of a small amount of amidic product (**1b′**) (Scheme 6). A small quantity of phenylglyoxal is formed by the partial hydrolysis of the intermediate (**D**), which on decarbonylation gave benzaldehyde.[1h,12] The *in situ* generated benzoyl radical from benzaldehyde in the presence of TBHP couples with the dimethylaminyl radical generated from HMPA to give *N*,*N*-dimethylbenzamide (**1b′**) as the side product (Scheme 6).



Scheme 6 Plausible mechanism for the synthesis of α-ketoamides.

Conclusion

In conclusion, we have developed a novel and efficient metal-free protocol for the synthesis of α-ketoamides from arylmethyl ketones and different alkylphosphoramides in the presence of TBAI as the catalyst and TBHP as the oxidant in a short period of time. A series of alkylphosphoramide having different functional groups have been utilised for the synthesis of corresponding α-ketoamide. This process tolerates a variety of functional groups and allows the synthesis of α-ketoamide derivatives in moderate to good yields. Based on the experimental findings, a plausible radical mechanism has been proposed for this transformation.

Typical procedure for the synthesis of *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (1a)

An oven-dried round bottom flask was charged with acetophenone (**a**) (60 mg, 0.5 mmol), ^{n}Bu$_4$NI (20mol%, 37 mg), HMPA (**1**) (268 mg, 1.5 mmol), chlorobenzene (2 mL), TBHP (70 wt% in H$_2$O) (6 equiv.). The flask was fitted with a condenser and the resultant reaction mixture was stirred in a pre-heated oil bath maintained at 130 ^{o}C. The reaction progress was monitored by TLC. After 45 minutes, the reaction mixture was cooled to room temperature. Then the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous Na_2SO_4. The solvent was then evaporated under reduced pressure and the residue was purified by column chromatography with an eluent hexane / ethylacetate (80 / 20) to afford the desired product (**1a**) in an isolated yield of 72% (63.7 mg).

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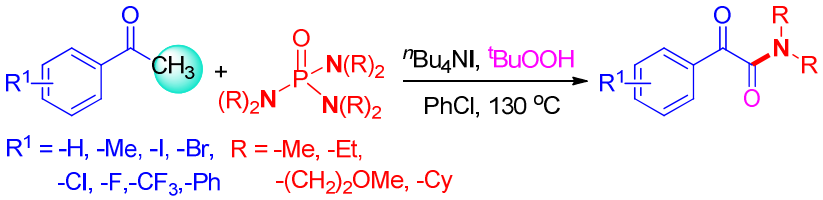
Transition metal-free synthesis of α-ketoamides from arylmethyl ketones and alkylphosphoramides

Ahalya Behera, Wajid Ali, Manisha Tripathy, Diptimayee Sahoo and Bhisma K. Patel*



Synthesis of α-ketoamides from arylmethyl ketones and hexalkylphosphoramides using TBAI as the catalyst and TBHP as the oxidant.