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Novel synthesis of cyclobutanone derivatives *via* dimetalation of iminium ions with the $TiCl_4$–trialkylamine reagent system†

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Received (in Cambridge, UK) 5th April 2001, Accepted 24th July 2001
First published as an Advance Article on the web 28th August 2001

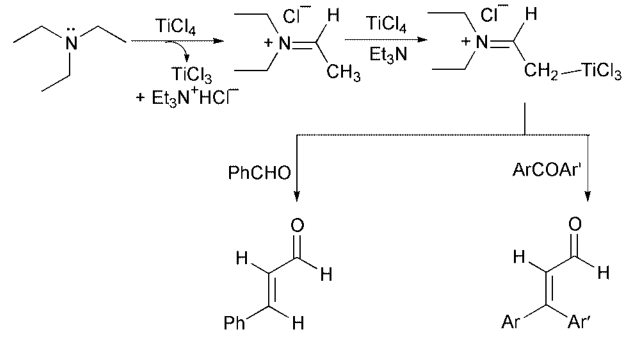
Iminium salts are generated *in situ*, react with $TiCl_4$–trialkylamines, and diaryl ketones to produce 3,3-diarylcyclobutanones in moderate to good yields.

The $TiCl_4$–R_3N combination is well-known to mediate aldol type condensation reactions[1] and oxidative coupling of certain ester enolates.[2] We have reported that the $TiCl_4$–R_3N reagent system is useful for the oxidative coupling of aryl methyl ketimines to 2,5-diarylpyrroles,[3a] for the direct metalation of alk-1-ynes,[3b] for the reductive coupling of imines and aromatic aldehydes,[3c] and for the oxidative coupling of *N*,*N*-dialkylarylamines.[3d] Also, it was observed that trialkylamines are oxidized to iminium ions by $TiCl_4$ with concomitant formation of $TiCl_3$.[3c,4] Herein, we wish to report that the iminium ions generated *in situ*,[5] undergo metalation followed by reaction with diaryl ketones to produce the corresponding 3,3-diarylcyclobutanones in moderate to good yields.

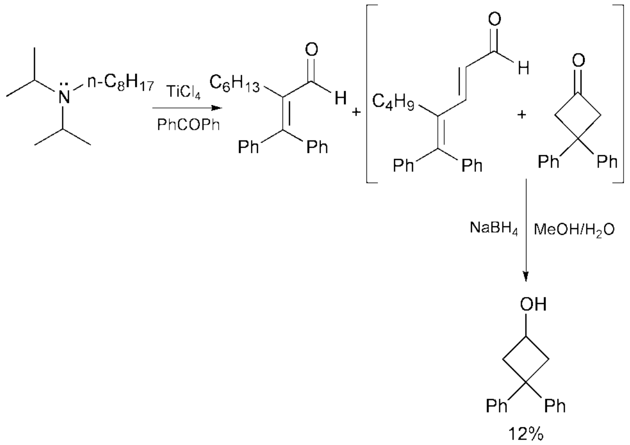
Metalation of iminium ions using $TiCl_4$ and its further reaction with PhCOPh produce α,β-unsaturated aldehydes (Scheme 1).[4]

We have examined the reaction of *N*,*N*-diisopropyl-*N*-ethylamine under these conditions. In this case, an inseparable mixture of the corresponding α,β-unsaturated aldehyde derivative and the cyclobutanone derivative was obtained. The use of *N*,*N*-diisopropyl-*N*-octylamine produced a better yield of the product mixture (Scheme 2).

Fortunately, the corresponding cyclobutanol could be readily separated after the reduction of the product mixture with $NaBH_4$–MeOH–H_2O (overall yield 12%). Attempts to optimize the reaction conditions to obtain better yields of the cyclobutanones using various *N*,*N*-diisopropyl-*N*-alkylamines were not fruitful. Therefore, we have examined the reactions of iminium ions prepared *in situ* using other methods. It was found that the iminium ions prepared through the oxidation of *N*,*N*-diisopropyl-*N*-benzylamine with I_2 gave better results. For example, in the reaction of the iminium ions with $TiCl_4$–*N*,*N*-diisopropyl-*N*-benzylamine and PhCOPh, the cyclobutanone derivative was obtained in 76% yield (Scheme 3).[6]



Scheme 1

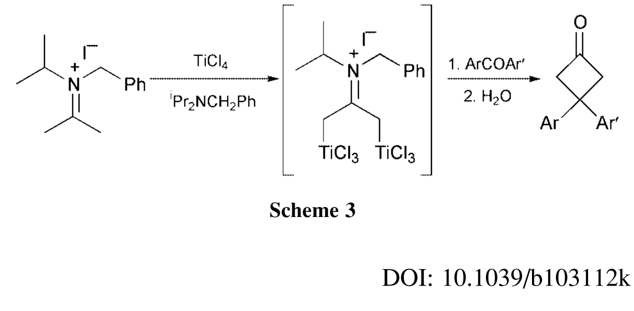


Scheme 2

When benzaldehyde was used as electrophile, the expected 3-arylcyclobutanone was not formed. Instead, only the dihydroxy ketone **7a** and the divinyl ketone **7b** were obtained in 58 and 11% yields respectively, besides some unidentified products. Earlier, such a reactivity was reported when the (2-siloxyallyl)silane was used as synthetic equivalent of acetone α,α′-dianion in the $TiCl_4$ mediated reaction with aromatic aldehydes.[7]‡

We have carried out several experiments to examine the scope and limitations of this transformation (Table 1). It was observed that the use of TMEDA in the place of *N*,*N*-diisopropyl-*N*-benzylamine gave the cyclobutanone derivative in poor yields (6%). Addition of PhCOPh initially or after the formation of the iminium ion gave no significant change to the results. Though the reaction works well at 25 °C, the yields of cyclobutanone are slightly better (10 to 20% more) under refluxing conditions. Dichloroethane was found to be the best solvent compared to CH_2Cl_2 and $CHCl_3$. When acetophenone was used as substrate, a complex mixture of products was obtained, possibly due to competing aldol type reactions.[8]

The formation of a cyclobutanone derivative may be tentatively explained by a mechanism involving the dimetalated iminium ion intermediate (Scheme 3). The reaction of 2 eq. of 3° amine and 1 eq. of I_2 would give the iminium iodide.[5] Deprotonation of the β-hydrogen atoms of the iminium ion using *N*,*N*-diisopropyl-*N*-benzylamine and further metalation with $TiCl_4$ could give the 1,3-dititanated iminium ion intermediate. The reaction of 1,3-dimetalated species with diarylketone would give the corresponding cyclobutanone (Scheme 3). However,



Scheme 3

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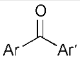
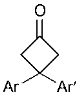
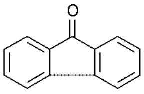
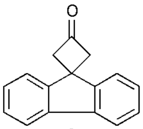
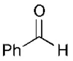
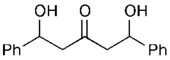
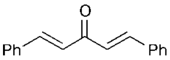
† Electronic supplementary information (ESI) available: ^{13}C NMR spectra of compounds **1a**, **2a**, **3a**, **4a**, **5a**, **6a**, **7a** and **7b**. See http://www.rsc.org/suppdata/cc/b1/103112k/

DOI: 10.1039/b103112k

Table 1 Reaction of iminium ions (Scheme 3) with $TiCl_4$–R_3N and ArCOAr′ or PhCHO

Entry	Substrate	Product[a]	Yield[b] (%)
			
1	Ar=Ar′=Ph **1**	**1a**	76
2	Ar=Ar′=4-MeC_6H_4 **2**	**2a**	71
3	Ar=Ar′=4-ClC_6H_4 **3**	**3a**	86
4	Ar=Ph Ar′=4-MeC_6H_4 **4**	**4a**	73
5	Ar=Ph Ar′=Ferrocenyl **5**	**5a**	51
6	 **6**	 **6a**	56
7	 **7**	 **7a**	58
		 **7b**	11

[a] The products were identified by ^1H, ^{13}C NMR, mass spectral and physical constant data and comparison with the reported data.[8] [b] The yields are based on the amount of ketone/aldehyde used.

the possibility of an alternative mechanism involving sequential metalation–addition reactions cannot be ruled out.

In conclusion, simple one pot methods of conversion of diaryl ketones to 3,3-diarylcyclobutanones from readily available starting materials have been developed. Previously, syntheses of such cyclobutanone derivatives have been reported *via* methods such as (i) the 2 + 2 cycloaddition of ketenes to diazomethane,[9] (ii) the 2 + 2 cycloaddition of dichloroketene to olefins,[10] and (iii) the 2 + 2 cycloaddition of ketiminium salts to olefins.[11] The one pot conversions described here involving a 1,3-dimetalated iminium ion intermediate, is a simple alternative to hitherto known methods of synthesis of cyclobutanone derivatives.[12] Moreover, it is anticipated that the interesting reactivity pattern of the titanium intermediates reported here should stimulate further research activities in this area.

We are grateful to the UGC and DST (New Delhi, India) for financial support. KNJ thanks CSIR and PB thanks UGC for fellowships. We are also thankful to the UGC for support under Special Assistance Program.

Notes and references

‡ ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in $CDCl_3$ unless otherwise stated and TMS was used as reference (δ = 0 ppm). The chemical shifts are reported in ppm on the δ scale relative to $CDCl_3$ (77.0 ppm). Melting points are uncorrected.

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6 *Representative procedure for the reaction of diaryl ketones*: to dichloroethane (25 mL) benzophenone (0.456 g, 2.5 mmol) and I_2 (0.63 g, 2.5 mmol) were added at 25 °C under N_2. *N*,*N*-diisopropyl-*N*-benzylamine (0.955 g, 5 mmol) was added and the mixture was refluxed at 95–100 °C for 2 h and brought to rt under N_2. $TiCl_4$ (1.65 mL of 1 : 1 solution of $TiCl_4$–CH_2Cl_2, 7.5 mmol) was added at 0 °C followed by *N*,*N*-diisopropyl-*N*-benzylamine (1.433 g, 7.5 mmol). It was stirred at 0 °C for 10 min and then refluxed at 95–100 °C for 6 h. The contents were brought to rt, then a saturated NH_4Cl solution (20 mL) was added and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with 5 M HCl (2 × 20 mL) to remove the unreacted amine, followed by water and brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. Unidentified less polar compounds and the unreacted ketone were eluted using 1 : 99 EtOAc–hexane mixture. The 3,3-diphenylcyclobutanone **1a** was eluted using 2 : 98 EtOAc–hexane (0.258 g, 76%). *Procedure for the reaction of benzaldehyde*: to dichloroethane (25 mL) I_2 (0.63 g, 2.5 mmol) was added at 25 °C under N_2. *N*,*N*-diisopropyl-*N*-benzylamine (0.955 g, 5 mmol) was added and the mixture was refluxed at 95–100 °C for 2 h and brought to rt under N_2. $TiCl_4$ (1.65 mL of 1 : 1 solution of $TiCl_4$–CH_2Cl_2, 7.5 mmol) was added at 0 °C followed by *N*,*N*-diisopropyl-*N*-benzylamine (1.433 g, 7.5 mmol). It was stirred at 0 °C for 10 min and then benzaldehyde (0.51 mL, 5 mmol) was added. The mixture was refluxed at 95–100 °C for 6 h. The contents were brought to rt, then a saturated NH_4Cl solution (20 mL) was added and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with 5 M HCl (2 × 20 mL) to remove the unreacted amine, followed by water and brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. Unidentified less polar compounds and the unreacted benzaldehyde were eluted using 1 : 99 EtOAc–hexane mixture. The divinyl ketone **7b** was eluted using 3 : 97 EtOAc–hexane mixture (0.054 g, 11%). The dihydroxy ketone **7a** was eluted using 6 : 94 EtOAc–hexane mixture (0.372 g, 58%).

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8 **1a**: mp 83–84 °C (lit.[9] mp 84–85 °C); IR (cm^{-1}): $\nu_{C=O}$ 1786; ^{13}C NMR δ 205.29, 147.29, 128.72, 126.76, 126.52, 60.57, 42.06; ^1H NMR δ 7.4–7.2 (m, 10H), 3.8 (s, 4H). **2a**: mp 71–73 °C; IR (cm^{-1}): $\nu_{C=O}$ 1786; ^{13}C NMR δ 205.65, 144.64, 136.02, 129.39, 126.65, 60.57, 41.43, 20.98; ^1H NMR δ 7.3–7.18 (m, 8H), 3.8 (s, 4H), 2.4 (s, 6H); mass: M^+ (*m*/*e*) 250. **3a**: mp 110–112 °C; IR (cm^{-1}): $\nu_{C=O}$ 1790, 1770; ^{13}C NMR δ 203.73, 145.23, 132.75, 128.95, 128.08, 60.49, 41.39; ^1H NMR δ 7.32–7.2 (m, 8H), 3.77 (s, 4H); mass: M^+ (*m*/*e*) 291. **4a**: mp 64–65 °C; IR (cm^{-1}): $\nu_{C=O}$ 1790; ^{13}C NMR δ 205.29, 147.59, 144.39, 136.10, 129.41, 128.70, 126.72, 126.45, 60.57, 41.76, 20.97; ^1H NMR δ 7.4–7.2 (m, 9H), 3.85 (s, 4H), 2.4 (s, 3H); mass: M^+ (*m*/*e*) 236. **5a**: mp 153–155 °C; IR (cm^{-1}): $\nu_{C=O}$ 1784, 1768; ^{13}C NMR δ 207.42, 147.34, 128.32, 126.55, 126.36, 98.44, 68.65, 68.28, 66.64, 61.42, 37.03; ^1H NMR δ 7.4–7.2 (m, 5H), 4.2 (s, 9H), 4.0–3.7 (m, 4H); mass: M^+ (*m*/*e*) 330. **6a**: mp 145–147 °C; IR (cm^{-1}): $\nu_{C=O}$ 1786; ^{13}C NMR δ 205.68, 150.05, 140.13, 128.04, 127.84, 121.85, 120.14, 58.95, 41.41; ^1H NMR δ 7.8–7.35 (m, 8H), 3.66 (s, 4H); mass: M^+ (*m*/*e*) 220. **7a**: mp 56–57 °C (lit.[13] mp 58–59 °C); IR (cm^{-1}): $\nu_{C=O}$ 1709, $\nu_{O\text{-}H}$ 3410; ^{13}C NMR δ 205.94, 140.89, 128.71, 128.12, 125.74, 78.95, 49.72; ^1H NMR δ 7.5–7.3 (m, 10H), 4.85 (dd, 2H), 2.8–2.6 (m, 4H). **7b**: mp 108–110 °C (lit.[14] mp 107–110 °C); IR (cm^{-1}): $\nu_{C=O}$ 1651, 1626; ^{13}C NMR δ 189.00, 143.32, 135.00, 130.51, 129.00, 128.42, 125.46; ^1H NMR δ 7.75 (d, 2H, J = 16 Hz), 7.65–7.4 (m, 10H), 7.09 (d, 2H, J = 16 Hz).

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