

Communications

Coupling Reaction of Acyl Cyanides with Titanium Tetrachloride-Indium System: Synthesis of 1,2-Diketones

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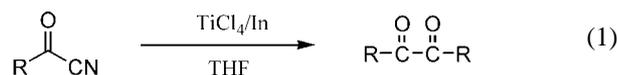
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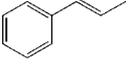
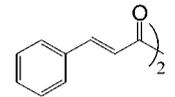
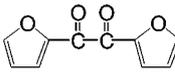
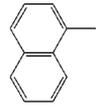
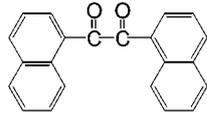
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Low-valent titanium species as reducing reagents for organic molecules and the synthetic utility of such species are well documented chemistry of wide interest.¹ In particular, the reductive coupling of aldehydes, ketones and imines using different low-valent titanium reagents is an important method for the construction of a vicinally functionalized carbon-framework.² The reduction of TiCl_4 to lower valent titanium species and the chemical reactivity of such species have been extensively studied.^{1(a)} Generally, reducing agents such as Li, Zn, Mg and Sm are used for the reduction of TiCl_4 .³ In continuation of our research efforts towards low-valent titanium reagents for organic transformations,⁴ we envisaged that a combination of TiCl_4 with indium could bring about the coupling of acyl cyanides. To our knowledge, there are no literature reports on the coupling of acyl cyanides to form 1,2-diketones by the use of low-valent titanium reagents. 1,2-Diketones have attracted much interest in organic synthesis as versatile intermediates with useful functional groups undergoing a wide variety of chemical transformation.⁵ Herein we wish to report a facile and efficient coupling of acyl cyanides to 1,2-diketones by treatment with TiCl_4/In system under mild conditions. We have investigated the coupling reactions of acyl cyanides with TiCl_4/In system in THF at room temperature and found that they can be smoothly coupled to give the corresponding 1,2-diketones (eq. 1). It has been shown that the cyano group is relatively more stable to low-valent titanium reagent than the carbonyl group and it could only be reduced under reflux for a long time.⁶ Recently, we have reported a reductive coupling



of acyl cyanides using indium.⁷ However, the reaction is slow and must be performed under sonication. The new reducing system was generated by the addition of indium powder to a stirred solution of titanium tetrachloride in THF under nitrogen. In order to explore the scope and limitations of this reagent system we have tested its applicability for the coupling reaction of various acyl cyanides bearing other functional groups. The reaction proceeded efficiently in moderate to good yields within 30 min at room temperature. The results are summarized in Table 1. However, coupling of acyl chlorides didn't give any significant desired product. The optimum ratio of reagents was found to be indium and TiCl_4 is 1 : 2.⁸ We examined a coupling reaction of acyl cyanides **1** with several systems such as TiCl_4/In , TiCl_4/Li , TiCl_4/Zn , TiCl_4/Mg and TiCl_4/Sm . Amongst the systems tested in this study, TiCl_4/In system gave the best results in terms of yield and reaction time and can be generally recommended, although other systems were also effective to some extent. The aromatic acyl cyanide was reductively coupled to give 1,2-diketone, but the application of this process to aliphatic acyl cyanide proved unsuccessful and only recovered starting material was isolated (entries 12 and 13). The functional group tolerance of this method is evident from entries 5-9 which show that ketone, ether, vinyl, chloro and bromo groups are unaffected under the reaction condi-

Table 1. Reductive coupling of acyl cyanides with TiCl₄/In system

| Entry | R | Products | Reaction time (min) | Yield (%) ^a |
|-------|--|--|---------------------|------------------------|
| 1 | Ph | (PhCO) ₂ | 30 | 73 |
| 2 | 2-CH ₃ C ₆ H ₄ | (2-CH ₃ C ₆ H ₄ CO) ₂ | 30 | 61 |
| 3 | 4-CH ₃ C ₆ H ₄ | (4-CH ₃ C ₆ H ₄ CO) ₂ | 30 | 71 |
| 4 | 4-t-BuC ₆ H ₄ | (4-t-BuC ₆ H ₄ CO) ₂ | 30 | 75 |
| 5 | 4-CH ₃ OC ₆ H ₄ | (4-CH ₃ OC ₆ H ₄ CO) ₂ | 30 | 72 |
| 6 | 4-BrC ₆ H ₄ | (4-BrC ₆ H ₄ CO) ₂ | 30 | 60 |
| 7 | 2-BrC ₆ H ₄ | (2-BrC ₆ H ₄ CO) ₂ | 30 | 43 |
| 8 | 2-ClC ₆ H ₄ | (2-ClC ₆ H ₄ CO) ₂ | 30 | 45 |
| 9 |  |  | 30 | 47 |
| 10 |  |  | 30 | 68 |
| 11 |  |  | 30 | 65 |
| 12 | CH ₃ (CH ₂) ₈ | — | 180 | 0 |
| 13 | Cyclohexyl | — | 180 | 0 |

^aIsolated yield.

tions. All the compounds obtained showed IR, NMR and mass spectral data compatible with the structure. Thus, we have been able to demonstrate the utility of easily accessible TiCl₄/In system as a convenient reagent for effecting chemoselective coupling of acyl cyanides. Although the role of titanium tetrachloride is not clear at the present stage, it is likely that reduction of titanium tetrachloride with indium provides low valent titanium species,⁹ which reacts with the acyl cyanide **1** to give the corresponding diketone **2**. We speculated that analogous to carbonyl coupling reaction, the acyl cyanide coupling probably would also proceed through a single electron transfer mechanism *via* an acyl radical intermediate. In principle, the intermediate RCO[•] can undergo dimerization to diketones by bimolecular process or can be quenched by a facile delivery of H[•] from the medium (THF) to give unimolecularly reduced aldehydes. It is also probable that the acyl radicals produced undergo decarbonylation before their dimerization.¹⁰ The lower yields (entries 7, 8 and 9) may be due to concomitant formation of aldehydes, as a result of competitive unimolecular reduction of acyl cyanides. The notable advantages of this methodology are mild reaction condition, fast reaction time, simple operation, and tolerance of other sensitive functional groups.

In conclusion, we believe the procedure using TiCl₄/In

system described here will present a useful and convenient alternative to the existing methods for the reductive coupling of acyl cyanides to diketones. Further investigations of TiCl₄/In system as reducing agent in organic synthesis are currently underway.

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- A typical procedure for the coupling of acyl cyanide is as follows: Indium powder (172 mg, 1.5 mmol) was added to titanium tetrachloride (569 mg, 3.0 mmol) in THF (15 mL) at room temperature under nitrogen atmosphere. The contents were stirred for 30 minutes at the same temperature and a dark-blue solution of the low-valent titanium-indium complex was obtained. To this solution, benzoyl cyanide (66 mg, 0.5 mmol) in THF (1 mL) was added and the reaction mixture was stirred for 30 minutes at room temperature under nitrogen. The resulting mixture was poured into water and the organic phase was separated and the aqueous phase was extracted with ether. The combined organic extract was washed with brine, dried over anhydrous MgSO₄ and concentrated. The residue was chromatographed on a silica gel column (hexane : ethyl acetate=10 : 1) to afford 1,2-diphenyl-ethane-1,2-dione (33 mg, 73%).
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