

New Low-valent Titanium Reagents for Dicarbonyl Coupling and their Use in a General Method of Annulation

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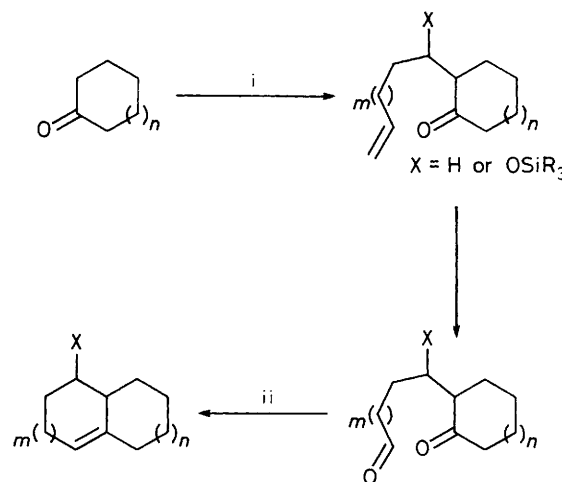
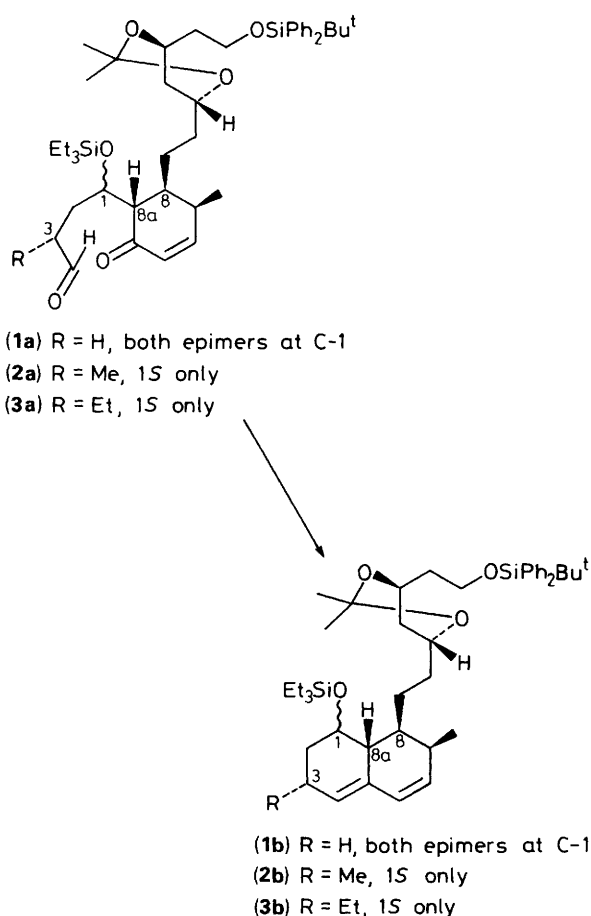
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Ketones carrying a chain that incorporates a suitably placed oxo function (aldehyde or ketone) undergo intramolecular dicarbonyl coupling when treated with a reagent prepared either from titanium trichloride and C_8K (relative molar ratio 1 : 2) or from titanium tetrachloride and sodium-naphthalene (relative molar ratio *ca.* 1 : 2.75); the reagent is used in excess (16 to 17 mol titanium halide per mol of dicarbonyl compound) and the process is the key step in a general method of annulation.

During attempts to synthesize the hypocholesterolemic agent (+)-compactin,¹ we prepared the enone aldehydes (**1a**) and treated the mixture under standard conditions² with the McMurry reagent made from titanium trichloride and zinc-copper couple. Little, if any, of the desired product (**1b**) was formed. Reagent prepared in the usual manner³ from titanium trichloride and lithium aluminium hydride also failed to give (**1b**); however, in the presence of triethylamine⁴ (**1b**) was produced, but only in 32% yield.[†] We then discovered that a reagent formed by mixing titanium trichloride (1.0 mol) and potassium graphite⁵ (C_8K) (2–2.1 mol), and used in excess [16–17 mol titanium trichloride per mol (**1a**)], affords (**1b**) in 85% yield. Under the same conditions (**2b**) and (**3b**) are obtained in 86% and 89% yield, respectively, and in no case

was there epimerization α to the aldehyde or ketone carbonyl groups (*i.e.*, at C-3 or C-8a). The need for excess of reagent is not due to complexation by oxygen substituents; this is evident from the fact that the same excess is required for optimum conversion of benzophenone into tetraphenylethylene (91% yield). The outcome of the reaction is very sensitive to the ratio of the components[‡] and, if more potassium graphite is used beyond that needed to produce (at least, formally) titanium(I), then the yield is low. However, an excess of the reagent mixture is definitely required (16–17 mol titanium trichloride per mol dicarbonyl compound).

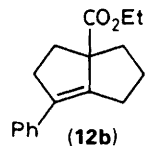
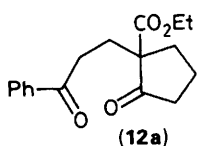
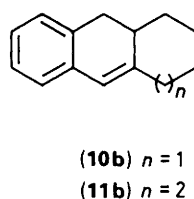
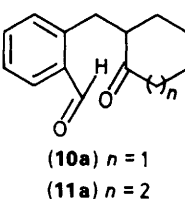
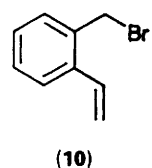
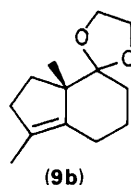
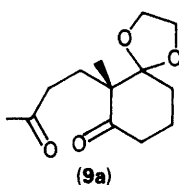
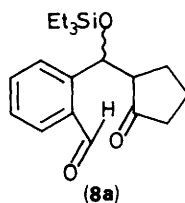
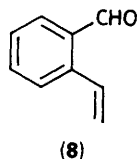
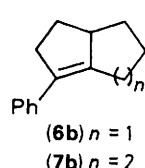
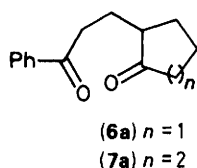
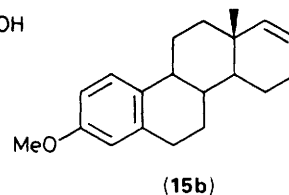
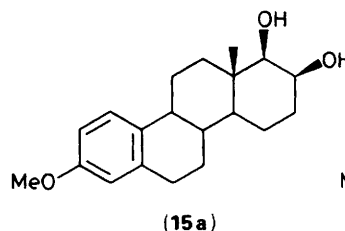
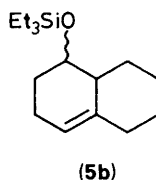
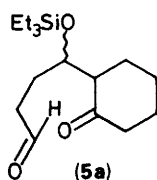
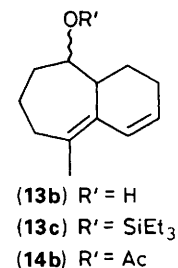
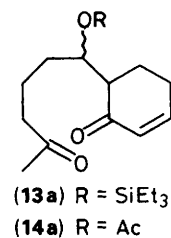
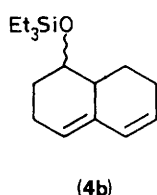
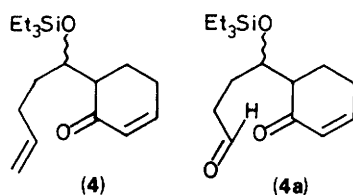
Although low-valent titanium species have been used to generate double bonds by intramolecular dicarbonyl coupling⁷ they do not appear to have been applied to compounds as extensively oxygenated as (**1a**)–(**3a**).⁸ Since the present reagent had worked in the demanding situation represented by (**1a**)–(**3a**), we have examined it further and have used it in the key step of the general annulation sequence shown in Scheme 1. We have also evaluated an equivalent reagent, generated from titanium tetrachloride (1.0 mol) and sodium-naphthalene (2.7–2.8 mol), which was used in excess (16–17 mol titanium tetrachloride per mol dicarbonyl substrate). This reagent is much easier to handle than that prepared from the trichloride and potassium graphite, both of which are air-sensitive solids. Of course, titanium tetrachloride (b.p. 136 °C) can be dispensed by syringe techniques, as can a solution of sodium-naphthalene. We prefer the



Scheme 1. Reagents and conditions: i, alkylation or aldol condensation and silylation; ii, $TiCl_3/C_8K$ or $TiCl_4/Na$ -naphthalene.

[‡] *E.g.*, (molar proportions, % yield): (**1a**) (1.0), $TiCl_3$ (10.0), C_8K (40.7), 0%; (**1a**) (1.0), $TiCl_3$ (10.0), C_8K (30.0), 30%; (**1a**) (1.0), $TiCl_3$ (17.1), C_8K (35.8), 85%.

[†] Yields in successive experiments were 30%, 34%, and 35%.

Table 1.^a

	Dicarbonyl compound	Method	Product	Yield/%
	(1a) ^b	A ^c	(1b)	85 ^b
	(1a)	B ^c	(1b)	71
	(2a)	A	(2b)	86 ^b
	(3a)	A	(3b)	89
(4) ^d	(4a) ^e	A	(4b)	82
	(5a) ^f	A	(5b)	64
	(6a) ^g	A	(6b)	86
	(7a) ^h	A	(7b)	87
(8) ⁱ	(8a) ^j	A	(8b)	50–51 ^k
	(8a)	C	(8b)	64–67 ^l
	(9a) ^m	B	(9b)	70
	(9a)	A	(9b)	75
(10) ⁿ	(10a) ^o	A	(10b)	81
	(11a) ^p	A	(11b)	86
	(12a) ^q	A	(12b)	61
	(12a)	B	(12b)	69
	(13a) ^r	A	(13b) ^s	59
	(13a)	A	(13c)	74
	(14a) ^t	B	(14b)	58
	(15a) ^u	D	(15b)	92 ^v

^a Yields refer to isolated compounds. The dicarbonyl compound was added to the titanium reagent over about 9 h at room temp. [(1a), (2a), (3a), (12a), (13a), (14a)] or at reflux [(4a), (5a), (6a), (7a), (8a), (9a), (10a), (11a)] and the mixture was refluxed for an additional 3–4 h. In certain cases the final reflux period was much longer: (5a) (30 h), (8a) (methods A and C, 31 h), (9a) (method A, 24 h, method B, 36 h). ^b See ref. 1. ^c Reagent system A: TiCl₃/C₈K/dme; B: TiCl₄/Na–naphthalene/thf; C: TiCl₃/C₈K/dioxane; D: TiCl₃/C₈K/diglyme. ^d Made by aldol condensation (80%) and silylation (83%). ^e From (4) by ozonolysis (60%). ^f From (4a) by hydrogenation (66%). ^g From phenyl vinyl ketone and cyclopentanone pyrrolidine enamine (79%). ^h From phenyl vinyl ketone and cyclohexanone pyrrolidine enamine (86%). ⁱ See ref. 10. ^j From (8) by aldol condensation (87%), silylation (85%), and ozonolysis (95–98%). ^k Yield with *threo* (8a) (*i.e.*, ring fusion hydrogen and siloxy group *trans*) was 50%, and with *erythro* (8a), 51%. ^l Yield with *threo* (8a) was 64%, with *erythro* (8a), 67%. ^m Prepared by alkylation of 2-methylcyclohexane-1,3-dione with 4-bromobutene, mono-ketalisation, and Wacker oxidation (*c.f.* ref. 8a). ⁿ From (8) by reduction (LiAlH₄, 83%) and treatment with PBr₃ (88%). See ref. 11. ^o From (10) and cyclohexanone pyrrolidine enamine (34%) and ozonolysis (84%). ^p Made analogously to (10a) (95%; 95%). ^q See ref. 12. ^r By aldol condensation (75%) using hex-5-enal, silylation (81%), and Wacker oxidation (79%). ^s Coupling product was isolated after desilylation (Bu₄NF). ^t Made analogously to (8a): yield for acetylation was 88%, and for Wacker oxidation, 87%. ^u See ref. 13. ^v Compound (15a) was added in one portion to the reagent and refluxing was continued for 40 h. When dme was used as the solvent the yield was only 12% after 16 h.

reagent based on the tetrachloride in those cases where separation of the product from naphthalene is easy. §

For the annulation sequence of Scheme 1 we prepared the dicarbonyl substrates (see Table 1) by standard methods. In this preliminary work, the pendant that includes the actual or potential carbonyl was attached by aldol condensation [(1a)—(5a), (8a), (13a), (14a)], alkylation [(9a), (10a), (11a)], or Michael addition [(6a), (7a), (12a)]. Usually, the additional step of ozonolysis or Wacker oxidation¹⁴ was required to introduce the second carbonyl. In each case, treatment with one of our titanium reagents¶ then served to complete the annulation sequence, and our results are shown in Table 1. The dicarbonyl coupling is slower if neither of the carbonyl groups is conjugated [cf. (4a) and (5a) of Table 1, and see footnote a of Table 1]. In one case [Table 1, (8a), method A] we isolated some vicinal diol, but we have not tried to adjust the temperature or time so as to stop the process at the diol stage.¹⁵ We did show, however, that our standard reagent will convert a diol into the corresponding alkene [Table 1, (15a)].

We have done a number of additional experiments to explore the characteristics of our reagents. Compounds (1a)—(3a) were too valuable for use as test substrates and so we examined compound (9a). This is readily available, it contains an acetal group, which is considered problematic for standard McMurry couplings,² and a homochiral form of (9a) had been reported^{8a} not to afford the desired product (9b) on treatment with titanium trichloride/zinc-copper couple. Surprisingly, our experiments with the titanium trichloride/potassium graphite and titanium tetrachloride/sodium-naphthalene systems [75% and 70% yield of (9b), respectively] as well as with the recently recommended $\text{TiCl}_3(\text{dme})_2$ /zinc-copper couple¹⁶ [70% yield of (9b)] (dme = dimethoxyethane) and the traditional reagent, titanium trichloride/zinc-copper couple² [72% yield of (9b)], showed that (9a) is not a very demanding substrate. The reaction product (9b) is inert to zinc-copper couple and to potassium graphite in refluxing dme, but an excess of potassium graphite must be avoided in the coupling step. With reagents derived from zinc-copper couple the yield is not sensitive to the ratio of the ingredients (within the range we examined), and use of commercial titanium trichloride or freshly prepared $\text{TiCl}_3(\text{dme})_2$ ¹⁶ gave very similar results.

§ Use of stoichiometric amounts of 1-(dimethylamino)naphthalene (ref. 9), which is, of course, extractable into acid, does not overcome the problem because some cleavage to naphthalene always occurs. When we sonicated (Branson Bath type B-12, 80 W) a catalytic amount of 1-(dimethylamino)naphthalene, titanium tetrachloride and sodium in tetrahydrofuran (THF) at room temp. for 24 h dissolution of the metal was incomplete.

¶ Typical experimental procedures (see also footnote a to Table 1): (a) C_8K (6.99 mmol) and TiCl_3 (3.37 mmol), weighed out under argon (preferably in a dry box) were added successively to dry dme (30 ml), and the stirred mixture was heated under argon for 2 h. A solution of the dicarbonyl compound (0.2 mmol) in dme (5 ml) was injected with stirring to the refluxing mixture over 9 h. (In some cases the addition was done at room temp.) Refluxing was continued for a further 24 h, the mixture was cooled to room temp. and filtered through a pad of Florisil with ether. (b) Sodium (10.20 mmol) was added under argon to a stirred solution of naphthalene (10.30 mmol) in THF (38 ml). Stirring was continued for 2 h and then TiCl_4 (freshly distilled from copper powder, 3.83 mmol) was added over about 10 min. The mixture was refluxed with stirring for 30 min, and a solution of the dicarbonyl compound (0.22 mol) in THF (5 ml) was injected over 9 h. Refluxing was continued for 36 h. The mixture was cooled to room temperature and filtered, under argon, through a pad of Florisil with ether.

While it is presently impracticable for us to use (1a)—(3a) to evaluate a range of ratios (substrate:titanium halide:reductant) for each of the known low-valent titanium reagents,^{3a,17} the titanium trichloride/potassium graphite and titanium tetrachloride/sodium-naphthalene systems reported here are the only ones, to our knowledge, whose generality has been demonstrated with compounds of the level of oxygenation represented by (1a)—(3a). Finally, we have tested the titanium trichloride/potassium graphite process for simple intermolecular coupling and, using the following ketones, obtained the expected coupled products in the yields indicated: benzophenone (91%), cyclohexen-2-one (75%, as a mixture of Z and E isomers), cyclododecanone (85%). Coupling of benzophenone was also done with the titanium tetrachloride/sodium-naphthalene reagent (87% yield). For these simple intermolecular processes we have not made a detailed study, but again the ratios (titanium halide:reductant) with both reagents appear to be important, at least for the test case of benzophenone.

All new compounds were fully characterized (including combustion analysis and/or exact mass measurement).

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