ChemComm

Chemical Communications

www.rsc.org/chemcomm

Number 5 | 7 February 2008 | Pages 513–636

ISSN 1359-7345

RSC Publishing

COMMUNICATION

Jean-Marc Gaudin and Pascal Millet

Transition metal-free addition of ketones or nitriles to 1,3-dienes

COMMUNICATION www.rsc.org/chemcomm | ChemComm

Transition metal-free addition of ketones or nitriles to 1,3-dienes†

Jean-Marc Gaudin* and Pascal Millet

Received (in Cambridge, UK) 4th October 2007, Accepted 8th November 2007
First published as an Advance Article on the web 15th November 2007
DOI: 10.1039/b715262k

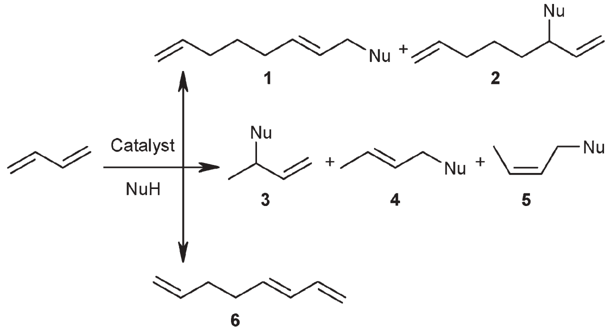
The simpler the better (or going green): The first examples of the catalytic addition of 1,3-dienes to simple ketones or nitriles are described. These reactions can be effected on a kilogram scale, representing the shortest access featuring a perfect atom economy to molecules of interest in the perfume industry.

Since 1967,[1] it is well known that by using transition metal catalysts, 1,3-dienes can react with a large variety of nucleophiles.[2] For example, it has been shown that 1,3-butadiene can react with a nucleophile (NuH) to afford different products depending on the catalyst used (Scheme 1). Thus, with water or an alcohol and using palladium with monodentate ligands, the reaction usually affords the linear telomer **1** with good selectivity. However, using bidentate ligands, a mixture of **3–5** can be obtained as major products.[3]

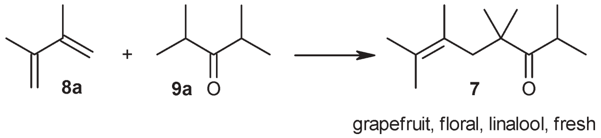
Very recently, Beller and co-workers[4] have shown that, by using appropriate palladium carbene catalysts, the selectivity can be completely switched in favour of either the isopropanol-telomer adduct **1** (Nu = O*i*Pr) or the dimer **6** (Scheme 1). It is interesting to note that more hindered alcohols such as *t*BuOH were considerably less reactive under the same conditions. The mechanism of these reactions has been well studied.[3,5]

Active methylene compounds react efficiently with 1,3-dienes and, by fine-tuning the catalysts, the outcome can be oriented towards the formation of 1 : 1 or 2 : 1 adducts. Numerous examples are known using malonates, cyanosulfones or acetoacetates.[2,6] Even if palladium remains the metal of choice, these reactions can be also catalyzed by nickel, platinum, rhodium or iridium, and very recently Li reported that gold and silver are also active catalysts.[7]

However, up to now, addition of 1,3-dienes to simple ketones or nitriles remains unreported, probably because the pK_a values of these nucleophiles are too high. In this context, we now report, the first examples of such reactions and moreover, we show that they can proceed in the absence of a transition-metal catalyst.



Scheme 1 Reactions of nucleophiles with 1,3-butadiene.



Scheme 2 Ideal reaction to build the odorant **7**.

Our initial motivation was to find an efficient and industrial synthesis of ketone **7** which is a powerful grapefruit odorant.[8] Thus, the reaction between 2,3-dimethyl-1,3-butadiene (**8a**) and 2,4-dimethyl-3-pentanone (**9a**) would represent the shortest access to **7**, with perfect atom economy (Scheme 2).

In 1991, Narula *et al.*,[9] and later Knochel *et al.*[10] described the addition of carbonyl or nitrile derivatives to styrenes, using NaH or *t*BuOK respectively. In our initial attempts to access **7**, we decided to test this latter base in amounts between 10 to 70 mol%. Moreover, in order to limit the possibility of a double addition (α and α′ to the carbonyl group), we used an excess of ketone **9a**.

The choice of the solvent turned out to be critical. Although DMSO is known to react with 1,3-dienes in the presence of *t*BuOK (1,3-pentadiene gave 40% of an isomeric mixture of hexadienes in 17 h at 55 °C, and 1,3-butadiene reacted even faster[11]), however this solvent gave a surprisingly good result (Table 1, entry 1).

A preliminary experiment with DMF as solvent gave a slower reaction compared to DMSO and a somewhat lower yield (Table 1, entry 2) while Et_3N, THF or *t*BuOH were totally inefficient (Table 1, entries 3–5). DMPU also worked very well (Table 1, entry 6), indicating that a polar aprotic solvent is clearly required in these reactions.

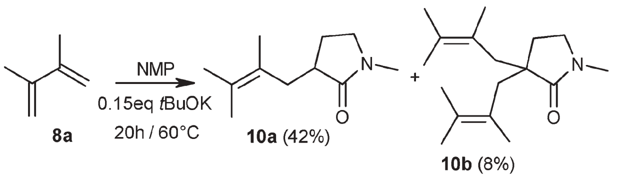
Table 1 Reaction of 2,3-dimethyl-1,3-butadiene (**8a**) and ketone **9a**

Entry	Diene **8a** (mmol)	Ketone **9a** (eq.)[a]	*t*BuOK (eq.)[a]	Solvent[b] (ml)	*t*(h)/ *T*(°C)	Yield of **7**[c] (%)
1	33	3	0.4	DMSO (40)	16/60	54
2	33	3	0.4	DMF (40)	48/60	48
3	33	3	0.4	Et_3N (40)	48/60	3
4	33	3	0.4	*t*-BuOH (40)	48/60	0
5	33	3	0.4	THF (40)	48/60	0
6	33	2	0.4	DMPU (40)	48/80	70
7	66	2	0.4	DMF (80)	72/60	63
8	66	2	0.4	DMF (80)	72/80	72
9	79	1.2	0.68	DMF (80)	60/90	81
10	633	1.2	0.55	DMF (160)	72/80	86
11	6330	1.2	0.55	DMF (1600)	72/80	83

[a] Equivalents relative to the diene. [b] DMSO = dimethyl sulfoxide, DMF = *N*,*N*-dimethylformamide, DMPU = *N*,*N*′-dimethylpropylene urea. [c] Yield of isolated product.

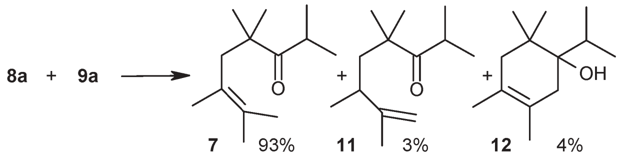
Firmenich SA, Corporate R&D Division, P. O. Box 239, CH-1211, Geneva 8, Switzerland. E-mail: jean-marc.gaudin@firmenich.com

† Electronic supplementary information (ESI) available: Experimental section and spectroscopic data. See DOI: 10.1039/b715262k



8a **10a** (42%) **10b** (8%)

Scheme 3 Reaction of 1-methyl-2-pyrrolidinone with 2,3-dimethyl-1,3-butadiene (**8a**).



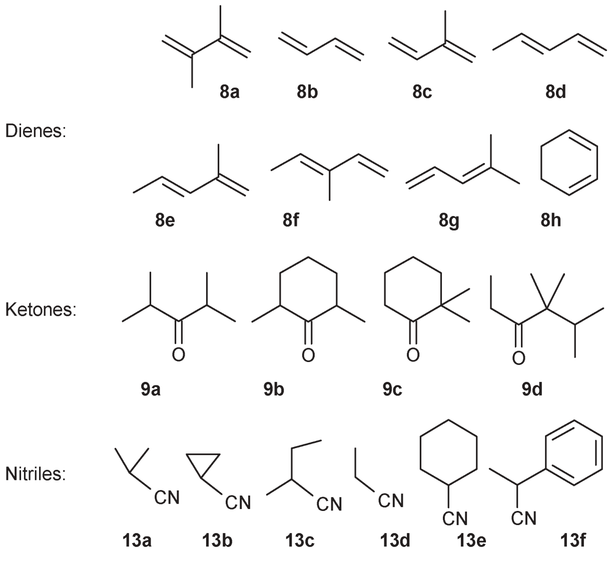
7 **11** **12**

Scheme 4 Two minor by-products identified during the kilogram scale production of **7** (GC%).

Because of its associated odour, DMSO is unsuitable for our purpose. Whereas 1-methyl-2-pyrrolidinone (NMP) does not have this drawback, it is even less suitable, as it is not completely inert and forms the mono- and diadducts **10a** and **10b** with 2,3-dimethyl-1,3-butadiene (**8a**) (Scheme 3)[10,12] in variable amounts (5 to 30%). Among the preferred solvents (DMF, DMSO, DMPU) we decided to select DMF for further optimisation.

Optimisation of the conditions allowed a decrease in the quantity of ketone **9a** to 1.2 equivalents without competition of the double addition (Table 1, entries 2, 7, 9) and a reduction in the amount of solvent with an increase in yield (Table 1, entries 9, 10).

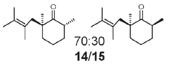
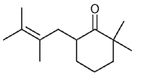
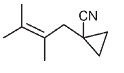
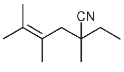
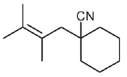
As the optimum temperature was found to be slightly higher than the boiling point of 2,3-dimethyl-1,3-butadiene (**8a**) (68–70 °C), the reaction was effected in a closed reactor. Scale-up of the reaction is possible (Table 1, entries 10, 11). An experiment on large scale reproducibly furnished more than 1 kg of isolated pure ketone **7** (83% yield). Fractional distillation allowed the isolation of two minor side-products: unsaturated ketone **11** and cyclohexanol **12** (Scheme 4). It is worth noting that almost no residue is formed.



8a **8b** **8c** **8d** **8e** **8f** **8g** **8h** **9a** **9b** **9c** **9d** **13a** **13b** **13c** **13d** **13e** **13f**

Scheme 5 Set of 1,3-dienes **8**, ketones **9** and nitriles **13** used.

Table 2 Reaction of **8a** with ketones **9b,c** or nitriles **13b,c,e**

Entry	Diene **8a** (mmol)	Ketone or nitrile (eq.)	*t*BuOK (eq.)[a,b]	*t*(h)/ *T*(°C)	Product	Yield[c] (%)
1	122	**9b** (1.23)	0.58	72 100	 70:30 **14/15**	61
2	122	**9c** (1.23)	0.58	72 100	 **16**	45
3	96	**13b** (0.75)	0.25	18 60	 **17**	45
4	96	**13c** (0.75)	0.25	45 60	 **18**	72
5	96	**13e** (0.75)	0.25	18 60	 **19**	76

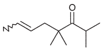
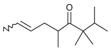
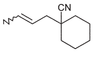
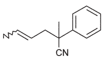
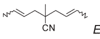
[a] Equivalents relative to **8a**. [b] DMF as solvent. [c] Yield of isolated product calculated on the starting material used by default.

In order to study the scope and limitations of this novel reaction, a series of experiments was effected using **8a** and various other ketones **9** and nitriles **13** (Scheme 5 and Table 2). It was found that nitriles react even better and more rapidly than ketones.

A series of reactions was then effected with **8b** (Table 3). This diene is much more reactive than **8a**; and products can be obtained at or below RT (Table 3, entries 1, 3, 5). It is also possible to direct the reaction towards either mono or dialkylation products, depending on the proportion of the starting material used (Table 3, entry 5).

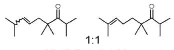
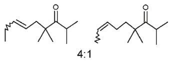
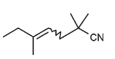
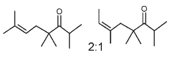
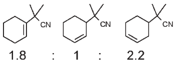
Other 1,3-dienes can also be employed (Table 4), and yields are generally good, although the products are often mixtures of regio and *E*/*Z* stereoisomers.[13] It is interesting to note that 2-methyl-1,3-pentadiene (**8e**) rapidly isomerises to 4-methyl-1,3-pentadiene (**8g**)

Table 3 Reaction between 1,3-butadiene **8b** with ketones **9** or nitriles **13**

Entry	Diene **8b** (mmol)[a]	Ketone or mitrile (eq.)	*t*BuOK (eq.)[b,c]	*t*(h)/ *T*(°C)	Product	Yield[d] (%)
1	80	**9a** (0.91)	0.15	7 5	 **20**[e] *E*:*Z*=50:50	74
2	80	**9d** (1.25)	0.15	96 50	 **21** *E*:*Z*=75:25	60
3	96	**13e** (0.76)	0.12	2 25	 **22** *E*:*Z*=88:12	80
4	100	**13f** (0.73)	0.12	6 80	 **23**[f] *E*:*Z*=75:25	71
5	600	**13d** (0.48)	0.09	15 20	 **24**[g] *E*,*E*:*E*,*Z* =70:30	63

[a] Due to the high volatility of **8b** these figures are approximate. [b] Equivalents relative to **8b**. [c] DMF as solvent. [d] Yield of isolated product calculated on the starting material used by default. [e] Contains 10% of alkene in the ω position. [f] Contains 15% of alkene in position 3. [g] Two other isomers (*Z*,*Z* and *E*,ω) are also present (3% each).

Table 4 Reaction of various 1,3-dienes **8** with ketone **9a** or nitrile **13a**

Entry	Diene (mmol)	Ketone or nitrile (eq.)	*t*BuOK (eq.)[a,b]	*t*(h)/ *T*(°C)	Product	Yield[c] (%)
1	**8e** (122)	**9a** (1.23)	0.58	72 100	 1:1 **25** (*E*:*Z*=4:1) / **26**	40
2	**8d** (79)	**9a** (1.20)	0.67	35 100	 4:1 **27** (60:40) **28** (65:35)	84
3	**8f** (96)	**13a** (0.75)	0.28	72 100	 **29** *E*:*Z*=70:30	72
4	**8c** (66)	**9a** (3)	0.41	16 40	 2:1 **30** **31**	77
5	**8h** (111)	**13a** (0.76)	0.25	15 60	 1.8 : 1 : 2.2 **32** **33** **34**	77

[a] Equivalents relative to diene. [b] DMF as solvent except for entry 4 where DMSO was used. [c] Yield of isolated product.

prior to the addition reaction, affording the products **25** (*E*/*Z* = 4/1) and **26** (Table 4, entry 1).

For unsymmetrical dienes **8d** or **8f**, the ketone or nitrile selectively reacts on the less substituted position (Table 4, entries 2, 3), whereas with isoprene **8c** poor selectivity is observed (Table 4, entry 4).

The reaction of 3-methyl-1,3-pentadiene (**8f**) with isobutyronitrile **13a** (Table 4, entry 3) led to a *E*/*Z* mixture of **29** in 72% yield. Two other unidentified isomers were present but represent less than 10% of the crude mixture.

In summary, we have shown that the addition of nitriles or ketones to 1,3-dienes proceeds very efficiently in the absence of a transition metal catalyst. To the best of our knowledge, such additions on these essential building blocks are unprecedented in the literature. This reaction can be effected on a kilogram scale without any polymerisation and is thus an excellent method for the efficient synthesis of γ,δ-enones and 3-butenylnitriles, following the main tenets of green chemistry (atom and step-economy).[14]

We wish to thank Mr R. Brauchli, Firmenich SA, for NMR analysis, Dr C. Fehr, Firmenich SA, and Dr R. L. Snowden, Firmenich SA, for their daily enthusiasm and support, but also all our colleagues for the fruitful discussions and correction of this manuscript.

Notes and references

1 E. Smutny, *J. Am. Chem. Soc.*, 1967, **89**, 6793–6794; S. Takahashi, T. Shibano and N. Hagihara, *Tetrahedron Lett.*, 1967, **8**, 2451–2453.

2 N. Yoshimura, in *Applied Homogeneous Catalysis with Organometallic Compounds*, ed. B. Cornils and W. A. Herrmann, VCH, Weinheim, 2000, vol. 1, p. 361; J. Tsuji, in *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, 1995, p. 422; J. M. Takacs, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon Press, Oxford, 1995, vol. 12, pp. 785–796.

3 K. Takahashi, A. Miyake and G. Hata, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 1183–1191; P. W. Jolly, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 283–295.

4 S. Harkal, R. Jackstell, F. Nierlich, D. Ortmann and M. Beller, *Org. Lett.*, 2005, **7**, 541–544; R. Jackstell, M. Gómez Andreu, A. Frisch, K. Selvakumar, A. Zapf, H. Klein, A. Spannenberg, D. Röttger, O. Briel, R. Karch and M. Beller, *Angew. Chem., Int. Ed.*, 2002, **41**, 986–989; R. Jackstell, S. Harkal, H. Jiao, A. Spannenberg, C. Borgmann, D. Röttger, F. Nierlich, M. Elliot, S. Niven, K. Cavell, O. Navarro, M. S. Viciu, S. P. Nolan and M. Beller, *Chem.–Eur. J.*, 2004, **10**, 3891–3900.

5 P. W. Jolly, R. Mynott, B. Raspel and K.-P. Schick, *Organometallics*, 1986, **5**, 473–481; A. Behr, G. V. Ilsemann, W. Keim, C. Krüger and Y.-H. Tsay, *Organometallics*, 1986, **5**, 514–518; F. Vollmüller, S. Klein, J. Krause, W. Mägerlein and M. Beller, *Eur. J. Inorg. Chem.*, 2000, **8**, 1825–1832.

6 A. Leitner, J. Larsen, C. Steffens and J. F. Hartwig, *J. Org. Chem.*, 2004, **69**, 7552–7557.

7 R.-V. Nguyen, X.-Q. Yao, D. Scott Bohle and C.-J. Li, *Org. Lett.*, 2005, **7**, 673–675.

8 J. M. Gaudin and P. Millet (Firmenich S.A.), *Int. Pat.*, WO 2004-IB 1607, May 13, 2004.

9 A. P. S. Narula, J. J. De Virgilio and W. L. Schreiber (International Flavors and Fragrances, Inc.), *Eur. Pat.*, 531636, Sep. 13, 1991; A. P. S. Narula, *Chem. Biodiversity*, 2004, **1**, 1992–2000.

10 A. L. Rodriguez, T. Bunlaksananusorn and P. Knochel, *Org. Lett.*, 2000, **2**, 3285–3287.

11 A. Argabright, J. E. Hofmann and A. Schriesheim, *J. Org. Chem.*, 1965, **30**, 3233–3234.

12 H. Pines, S. V. Kannan and J. Simonik, *J. Org. Chem.*, 1971, **36**, 2311–2315.

13 Detailed analysis of the isomer distributions based on the NMR spectra was difficult; however, hydrogenation of these mixtures afforded the corresponding saturated compounds in high purity.

14 M.-Y. Ngai, J.-R. Kong and M. Krische, *J. Org. Chem.*, 2007, **72**, 1063–1072, and references cited therein.