A novel cyclization reaction between 2,3-bis(trimethylsilyl)buta-1,3-diene and acyl chlorides with straightforward formation of polysubstituted furans†

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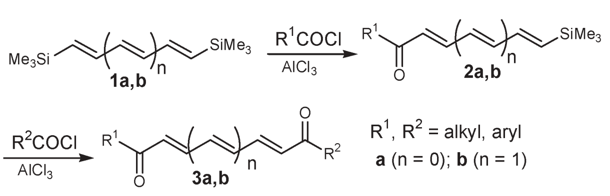
A novel cyclization process of 2,3-bis(trimethylsilyl)buta-1,3-diene with various acyl chlorides in the presence of aluminium trichloride affords 2,5-disubstituted or 2,3,5-trisubstituted furans in short reaction time; a subsequent acylation process of the furan ring occurs if the reaction time is prolonged.

In the frame of our studies dealing with synthesis of polyconjugated compounds,[1] we have extensively used unsaturated silanes as convenient starting materials.[2] Among them, (1*E*,3*E*)-1,4-bis(trimethylsilyl)buta-1,3-diene **1a** and (1*E*,3*E*,5*E*)-1,6-bis(trimethylsilyl)hexa-1,3,5-triene **1b** were subjected to formal cross-coupling processes[2f,g] and to substitution reactions with various electrophiles.[2a–c,e] In particular, we reported a convenient approach to ketosilanes with a conjugated (all-*E*) diene **2a** or triene **2b** structure *via* a highly chemoselective substitution of one trimethylsilyl group of the butadiene **1a** or hexatriene **1b** with acyl chlorides in the presence of $\mathrm{AlCl_3}$. Subsequent substitution of the second silyl group with another acyl chloride in the same reaction flask led to the corresponding dicarbonyl compounds with a conjugated diene **3a** or triene **3b** structure (Scheme 1).[2a] This methodology was successfully applied to the synthesis of several compounds of biological interest[2b,f] and to precursors of more extended polyenes.[2e] With this background, we addressed our attention to the acylation reaction of 2,3-bis(trimethylsilyl)buta-1,3-diene **4**. The butadiene **4** is easily available by various synthetic methodologies[3] but, with the exception of Diels–Alder reactions,[3d,e] addition of chlorocarbenes[4] and polymerization processes,[5] its reactivity has not yet been explored. Now we wish to report that the 2,3-bis-substituted diene **4** with the silyl groups in the internal positions in the reaction with the $\mathrm{ArCOCl/AlCl_3}$ electrophile follows a different and very useful synthetic pathway.



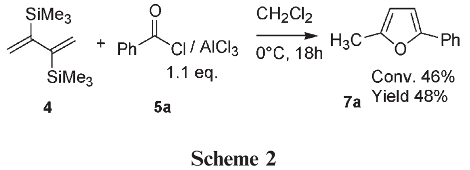
Scheme 1

As a starting point we studied the reaction of **4**[6] with the benzoyl chloride **5a**/aluminium trichloride complex, following the protocol described for the corresponding reaction of 1,4-bis(trimethyilsilyl)buta-1,3-diene **1a**.[2a] Accordingly, the freshly prepared benzoyl chloride **5a**/$\mathrm{AlCl_3}$ complex was slowly added to a solution of the diene **4** in 1.1:1 molar ratio, maintaining the temperature at 0 °C. After 18 h reaction time, **4** was only partially converted (46%) and the unexpected 2-methyl-5-phenylfuran **7a** (Scheme 2) was isolated in 48% yield after work-up and chromatography on silica gel column.[7]

Functionalized furans are common structural units in many natural molecules and pharmaceuticals,[8] flavours and fragrance compounds[9] and are broadly used as building blocks in organic synthesis[10] and materials science.[11] Common synthetic approaches are based either on cyclization of acyclic precursors or on transformation of furan rings by various functionalization processes.[12] Much attention has been paid to the former type of strategy, because of its broader potential and versatility.[13] In view of these considerations, we decided to investigate the reaction of Scheme 2 as a novel method for the synthesis of functionalized furans.

Different experimental conditions were tested to lead the reaction to completion. We found that a 1 : 2 molar ratio between the starting diene **4** and the benzoyl chloride **5a**/$\mathrm{AlCl_3}$ complex was necessary to complete the conversion of **4** affording, after 18 h reaction time, **7a** in 40% yield together with two regioisomeric products **8a**,**b** (15% yield), deriving from the acylation of the furan ring (Scheme 3). A further increase of the **4** : **5a**/$\mathrm{AlCl_3}$ ratio to 1 : 4 led, after a comparable reaction time, to the complete acylation of **7a** affording exclusively **8a**,**b** (62% yield) (Scheme 3). Higher yield of 2,5-disubstituted furan **7a** (56%) was obtained by increasing the **4** : **5a**/$\mathrm{AlCl_3}$ ratio up to 1 : 6 and shortening the reaction time (40 min) to prevent further acylation of the furan ring (Scheme 3).

A simple change of the experimental conditions allowed us to carry out the reaction with a more convenient stoichiometry: slow addition of the diene **4** to the pre-formed benzoyl chloride **5a**/$\mathrm{AlCl_3}$ complex in 1 : 1.5 **4** : **5a**/$\mathrm{AlCl_3}$ molar ratio at 0 °C followed by



Scheme 2

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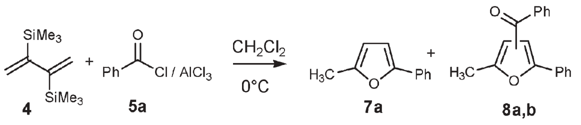
† Electronic supplementary information (ESI) available: Spectral data for all the furans synthesized and detailed experimental procedures. NOE experiments for compounds **6a–e**. See DOI: 10.1039/b705257j



$4:5a$ / $AlCl_3$	Time	Yield **7a**	Yield **8a,b**
1:2	18h	40%	15%
1:4	22h	0%	62%
1:6	40 min	56%	0%

Scheme 3

immediate quenching with a saturated solution of ammonium chloride led to reaction completion without further acylation of the furan ring. The furan **7a** was isolated as the sole reaction product in 63% yield by silica gel column chromatography.[14] GC-MS analysis of the reaction mixture before quenching and chromatographic purification revealed the presence of a mixture of **7a** and a trimethylsilyl-substituted **7a**, as already observed in the first experiment described.[7] Different experimental conditions had to be used to isolate this elusive silylated intermediate: quenching the reaction with a sodium carbonate saturated aqueous solution and chromatographic purification on basic alumina column afforded, besides furan **7a** (43% yield), a silylated derivative (21% yield), which was identified *via* ^{1}H NMR spectroscopy as 2-methyl-3-trimethylsilyl-5-phenyl furan **6a**. The position of the trimethylsilyl group on the furan ring was unambiguously determined by NOE experiments (see ESI†). From these data it seems reasonable that **6a** is formed as the first cyclization product, which then undergoes an easy desilylation in the acidic work up conditions and during the chromatography on silica gel column (Scheme 4).

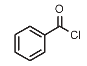
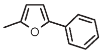
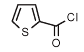
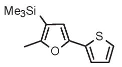
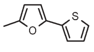
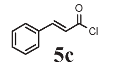
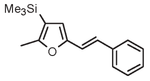
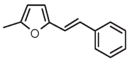
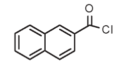
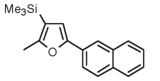
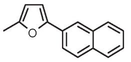
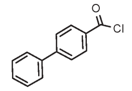
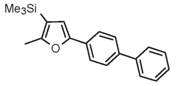
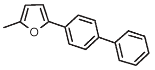
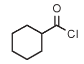
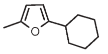
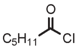
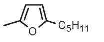
The reaction was extended to various acyl chlorides **5b–g** in similar experimental conditions (Scheme 4) and the results are summarized in Table 1.

When acyl chlorides **5b–e** were used (entries 2–5, Table 1), the corresponding silylated furans **6b–e**, whose structure was confirmed by NOE experiments, survived work-up and silica gel chromatographic purification and were isolated as the sole reaction products. They were subsequently subjected to quantitative desilylation in the presence of BF_3·etherate (Scheme 4). An increase of the acylation complex : diene ratio to 2 : 1 and to 3 : 1 was necessary for chlorides **5e** and **5c**, respectively, to optimize the reaction yields, and longer reaction times were needed in the case of the acyl chlorides **5b** and **5c** to lead the reaction to completion.

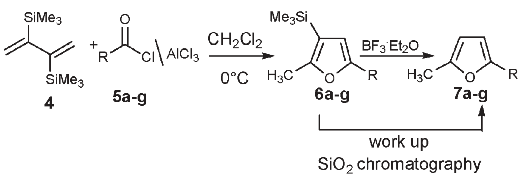
Although further studies are necessary to elucidate the mechanism of the process, the tentative pathway reported in Scheme 5 would involve: (i) acylation of diene **4** at the terminal carbon atom with formation of allyl cation **A**;[15](ii) deprotonation of **A** with formation of bis(trimethylsilyl) ketodiene **B**; (iii) protonation of **B** to generate allyl cation **C**;[15] (iv) cyclization of **C** to cyclic allyl cation **D**;[15] (v) desilylation of **D** affording the silylated furan **6a**.

In summary, we have reported our preliminary results on a novel cyclization process of the bis-silylated diene **4** and acyl chlorides promoted by aluminium trichloride, which appears suitable as a general protocol for the synthesis of 2,5-disubstituted and, in many cases, 2,3,5-trisubstituted furans. The method compares well with other cyclization processes for the synthesis

Table 1 Synthesis of polysubstituted furans

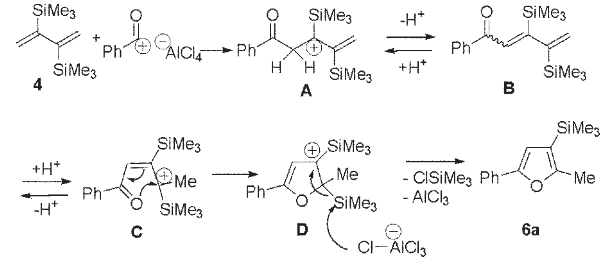
Entry	RCOCl	**5**/$AlCl_3$ equiv.	Silylated furan **6**	Furan **7**
1	 **5a**	1.5	—	 **7a** (63%)
2	 **5b**	1.5	 **6b** (52%)[a]	 **7b** (52%)
3	 **5c**	3[b]	 **6c** (81%)	 **7c** (81%)
4	 **5d**	1.5	 **6d** (60%)[c]	 **7d** (59%)
5	 **5e**	2[d]	 **6e** (74%)	 **7e** (73%)
6	 **5f**	1.5	—	 **7f** (72%)
7	 **5g**	1.5	—	 **7g** (50%)

[a] Reaction time 95 min including diene addition (20 min). [b] **4** : **5c**/$AlCl_3$ ratio = 1 : 3 was necessary to optimize the reaction yield (1 : 1.5 ratio and 1 : 2 ratio afforded 32 and 40% yield, respectively). [c] Reaction time 50 min including diene addition (20 min). [d] **4** : **5e**/$AlCl_3$ ratio = 1 : 2 was necessary to lead reaction to completion



R = (a) phenyl, (b) 2-thienyl, (c) 2-stiryl, (d) 2-naphtyl, (e) 4-biphenyl, (f) ciclohexyl, (g) hexyl

Scheme 4



Scheme 5

of substituted furans, in view of the easy experimental procedure and availability of starting compounds. The isolation, in many cases, of 3-trimethylsilyl-substituted furans represents another advantage of our approach, in consideration of the possibility, explored in the recent literature,[12b] to use the trimethylsilyl group for the regioselective introduction of functional groups on the furan ring.

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Notes and references

1 For a recent review, see: F. Babudri, G. M. Farinola and F. Naso, *J. Mater. Chem.*, 2004, **14**, 11.

2 (*a*) F. Babudri, V. Fiandanese, G. Marchese and F. Naso, *J. Chem. Soc., Chem. Commun.*, 1991, 237; (*b*) F. Babudri, V. Fiandanese and F. Naso, *J. Org. Chem.*, 1991, **56**, 6245; (*c*) F. Babudri, V. Fiandanese, F. Naso and A. Punzi, *Synlett*, 1992, 221; (*d*) G. M. Farinola, V. Fiandanese, L. Mazzone and F. Naso, *J. Chem. Soc., Chem. Commun.*, 1995, 2523; (*e*) F. Babudri, A. R. Cicciomessere, G. M. Farinola, V. Fiandanese, G. Marchese, R. Musio, F. Naso and O. Sciacovelli, *J. Org. Chem.*, 1997, **62**, 3291; (*f*) F. Babudri, G. M. Farinola, V. Fiandanese, L. Mazzone and F. Naso, *Tetrahedron*, 1998, **54**, 1085; (*g*) F. Babudri, G. M. Farinola, F. Naso and D. Panessa, *J. Org. Chem.*, 2000, **65**, 1554; (*h*) F. Babudri, G. M. Farinola, L. C. Lopez, M. G. Martinelli and F. Naso, *J. Org. Chem.*, 2001, **66**, 3878; (*i*) R. Ancora, F. Babudri, G. M. Farinola, F. Naso and R. Ragni, *Eur. J. Org. Chem.*, 2002, 4127.

3 (*a*) H. Bock and H. Seidl, *J. Am. Chem. Soc.*, 1968, **90**, 5694; (*b*) R. F. Cunico and Y.-K. Han, *J. Organomet. Chem.*, 1979, **174**, 247; (*c*) H. J. Reich, K. E. Yelm and I. L. Reich, *J. Org. Chem.*, 1984, **49**, 3438; (*d*) P. J. Garratt and A. Tsotinis, *Tetrahedron Lett.*, 1986, **27**, 2761; (*e*) H. Reich, I. L. Reich, K. E. Yelm, J. E. Holladay and D. Gschneider, *J. Am. Chem. Soc.*, 1993, **115**, 6625; (*f*) T. Takahashi, Z. Xi, R. Fisher, S. Huo, C. Xi and K. Nakajima, *J. Am. Chem. Soc.*, 1997, **119**, 4561.

4 W. E. Billups, M. M. Haley, R. Boese and D. Bläser, *Tetrahedron*, 1994, **50**, 10693.

5 Y.-X. Ding and W. P. Weber, *J. Organomet. Chem.*, 1988, **341**, 267.

6 The diene **4** employed for our reactions was prepared according to ref. 3*a*.

7 GC-MS analysis of the reaction mixture at different reaction times revealed the presence of a second product with molecular mass corresponding to that of **7a** with an hydrogen atom substituted by a trimethylsilyl group. This compound, subsequently identified as 2-methyl-3-trimethylsilyl-5-phenyl furan **6a**, was not isolated as it was converted into **7a** during work-up and chromatographic purification on silica gel column (see below and ESI†).

8 *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katrizky, C. W. Rees and E. F. V. Scriven, Pergamon, New York, 1996, vol. 2; pp. 259–295 (R. Benassi), pp. 297–350 (H. Heaney), pp. 351–393 (W. Friedrishsen), pp. 395–436 (B. A. Keay); X.-L. Hou, Z. Yang and H. N. C. Wong, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and T. L. Gilchrist, Pergamon, Oxford, 2003, vol. 15, pp. 167–205; D. L. Wright, in *Progress in Heterocyclic Chemistry*, ed. G. Gribble and J. Joulet, Pergamon, Oxford, 2005, vol. 17, pp. 1–32; X.-L. Hou, Z. Yang, K.-S. Yeung and H. N. C. Wong, in *Progress in Heterocyclic Chemistry*, ed. G. Gribble and J. Joulet, Elsevier Science, Amsterdam, 2005, vol. 17, pp. 142–171.

9 *Common Fragrance and Flavour Materials*, ed. K. Bauer and D. Garbe, VCH, Weinheim, 1985.

10 B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795; H.-K. Lee, K.-F. Chan, C.-W. Hui, H.-K. Yim, X.-W. Wu and H. N. C. Wong, *Pure Appl. Chem.*, 2005, **77**, 139.

11 C.-F. Lee, L.-M. Yang, T.-Y. Hwu, A.-S. Feng, J.-C. Tseng and T.-Y. Luh, *J. Am. Chem. Soc.*, 2000, **122**, 4992; C.-F. Lee, C.-Y. Liu, H.-C. Song, S.-J. Luo, J.-C. Tseng, H.-H. Tso and T.-Y. Luh, *Chem. Commun.*, 2002, 2824; M. D. Burke, E. M. Berger and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 14095; H.-C. Lin, W.-Y. Lin, H.-T. Bai, J.-H. Chen, B.-Y. Jin and T.-Y. Luh, *Angew. Chem., Int. Ed.*, 2007, **46**, 897.

12 For selected reviews on furan synthesis, see: (*a*) X. L. Huo, H. Y. Cheung, T. Y. Hong, P. L. Kwan, T. H. Lo, S. P. Tong and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955; (*b*) B. A. Keay, *Chem. Soc. Rev.*, 1999, **28**, 209; (*c*) T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2849; R. C. D. Brown, *Angew. Chem., Int. Ed.*, 2005, **44**, 850; (*d*) F. S. Kirsh, *Org. Biomol. Chem.*, 2006, **28**, 2076.

13 For selected examples of recent work: P. Forgione, P. D. Wilson and A. G. Fallis, *Tetrahedron Lett.*, 2000, **41**, 17; S. Ma and J. Zhang, *Chem. Commun.*, 2000, 117; K. Takai, R. Morita and S. Sakamoto, *Synlett*, 2001, 1614; J. M. Auerrocoechea, E. Perez and M. Solay, *J. Org. Chem.*, 2001, **66**, 564; A. V. Kel'in and V. Gevorgyan, *J. Org. Chem.*, 2002, **67**, 95; Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. D. Milton, M. Hidai and S. Uemura, *Angew. Chem., Int. Ed.*, 2002, **42**, 2861; S. Ma, J. Zhang and L. Lu, *Chem. Eur. J.*, 2003, **9**, 2447; A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli and L. M. Parisi, *Tetrahedron*, 2003, **59**, 4661; M. Nakamura, M. Yamane, H. Sakurai and N. Koichi, *Heterocycles*, 2003, **59**, 333; J. Tae and K.-O. Kim, *Tetrahedron Lett.*, 2003, **44**, 2125; A. W. Stromek, A. V. Kel'in and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2004, **43**, 2280; X. Han and R. A. Widenhoefer, *J. Org. Chem.*, 2004, **69**, 1738; C.-K. Jung, J.-C. Wang and M. J. Krische, *J. Am. Chem. Soc.*, 2004, **1265**, 4118; T. Yao, X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 11164; C. P. Casey and N. A. Strotman, *J. Org. Chem.*, 2005, **70**, 2576; K. Y. Lee, M. J. Lee and J. N. Kim, *Tetrahedron*, 2005, **61**, 8705; H. Imagawa, T. Kurisaki and M. Nishizawa, *Org. Lett.*, 2005, **7**, 451; A. Sniady, K. A. Wheeler and R. Dembinski, *Org. Lett.*, 2005, **7**, 1769; M. H. Suhre, M. Reif and S. F. Kirsch, *Org. Lett.*, 2005, **7**, 3925; Y. Liu, F. Song, Z. Song, M. Liu and B. Yan, *Org. Lett.*, 2005, **7**, 5409; T. Yao, X. Zhang and R. C. Larock, *J. Org. Chem.*, 2005, **70**, 7679; C.-Y. Zhou, P. W. Chan and C.-M. Che, *Org. Lett.*, 2006, **8**, 325; B. Xu and G. B. Hammond, *J. Org. Chem.*, 2006, **71**, 3518.

14 The experimental procedure used was the following: a CH_2Cl_2 solution (18 ml) of freshly distilled benzoyl chloride **5a** (0.319 g, 2.27 mmol) was added, under a nitrogen atmosphere, to a cold (0 °C) stirred suspension of anhydrous $AlCl_3$ (0.303 g, 2.27 mmol) in 6 ml of CH_2Cl_2. When the mixture became clear, a CH_2Cl_2 solution (6 ml) of 2,3-bis(trimethylsilyl)buta-1,3-diene **4** (0.300 g, 1.51 mmol) was slowly (about 20 min) added maintaining the temperature at 0 °C. Immediately after addition completion, the reaction was quenched with saturated aqueous NH_4Cl solution (30 ml) and extracted with CH_2Cl_2 (3×40 ml). The organic extracts were washed several times with saturated aqueous Na_2CO_3 solution, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (petroleum ether–ethyl acetate 9.8 : 0.2 as eluent) obtaining **7a** as a white solid (0.150 g, 63% yield) which was fully characterized by NMR spectroscopy and mass spectrometry (see ESI†).

15 The stabilizing effect of silyl groups on β carbocations is well documented (β effect) while the effect of silyl substituents in α position is still debated: see, for example, *Silicon in Organic, Organometallic and Polymer Chemistry*, ed. M. A. Brook, Wiley Interscience, New York, 2000, pp. 483–496.