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Reinvestigation of the fluoride-triggered condensation of allyltrimethylsilane with cinnamonitrile: 'abnormal Sakurai' and sequential 'abnormal Sakurai'–Michael–Thorpe Ziegler side reactions†

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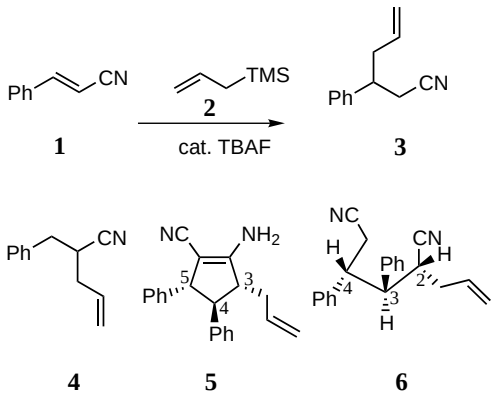
Abstract—Together with the expected 1,4-adduct, three by-products are generated in the fluoride-triggered condensation of allyltrimethylsilane with cinnamonitrile: the 1,3 adduct, an acyclic dinitrile and a cyclopentenaminonitrile issuing, respectively, from 'abnormal Sakurai', 'abnormal Sakurai'–Michael and 'abnormal Sakurai'–Michael–Thorpe Ziegler side reactions.

The conjugate addition of allylsilanes to electrophilic alkenes, referred to as Sakurai–Hosomi reaction has been recognized as a particularly efficient method of C–C bond formation, and has played an important role in the area of synthetic organic chemistry.[1] In 1986, Majetich et al. reported that the condensation of cinnamonitrile (**1**) with allyltrimethylsilane (**2**), promoted by a catalytic amount of *n*-Bu_4NF (TBAF) furnished the 1,4-adduct **3** with a 65% yield.[2] In connection with our sustained synthetic efforts in the cephalotaxine series,[3] we recently reinvestigated this condensation to assess its utility in the construction of this alkaloid. In this paper, we show that together with adduct **3**, three unexpected by-products **4**, **5** and **6** are in fact generated in the fluoride-triggered addition of **1** to **2**, the ratio of which depended essentially on the time of addition and the concentration of the reagents (Scheme 1).

Surprisingly, when the condensation of **1** with **2** was conducted under the reaction conditions reported by Majetich[2] (*dropwise* addition at 20°C of a 1 M solution of 3 equiv. of **2** and 3 equiv. of HMPA in DMF to a 0.6 M solution of 1 equiv. of **1** and 0.1 equiv. of TBAF in DMF, followed by 15 min stirring at 20°C and hydrolytic workup with MeOH and HCl), the main product characterized was invariably the cyclopentene derivative **5** (20–30% yield), accompanied by varying quantities of acyclic by-product **6** (0–10% yield) and only a minute amount of adduct **3** (ca. 5% yield). Compound **5**,[4] a low melting point (58–59°C) solid, was



Scheme 1.

Keywords: mechanisms; Michael reactions; rearrangements; Sakurai reactions; Thorpe and Thorpe–Ziegler reactions.

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† This paper is dedicated to Professor Gilbert Stork on the occasion of his 80th birthday.

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assigned a molecular formula of $C_{21}H_{20}N_2$ established by elemental analysis and mass spectroscopy, corresponding to the formal condensation of one allyl unit with two molecules of cinnamonitrile (**1**). The gross structure of **5** was deduced from detailed analysis of the ^1H and ^{13}C NMR data, aided with 2D NMR experiments (^1H–^1H COSY, HMQC and HMBC) and of the IR spectrum which revealed the presence of a β-enaminonitrile moiety (ν(NH) at 3480 and 3363 cm^{-1}, ν(CN) at 2185 cm^{-1} and ν(C=C) at 1639 cm^{-1}). Finally, the full structure of **5**, including the relative configuration of the three stereogenic centers was defined as (3*R**,4*S**,5*R**)-3-allyl-2-amino-4,5-diphenyl-cyclopent-1-enecarbonitrile by means of a single crystal X-ray diffraction analysis (Fig. 1).

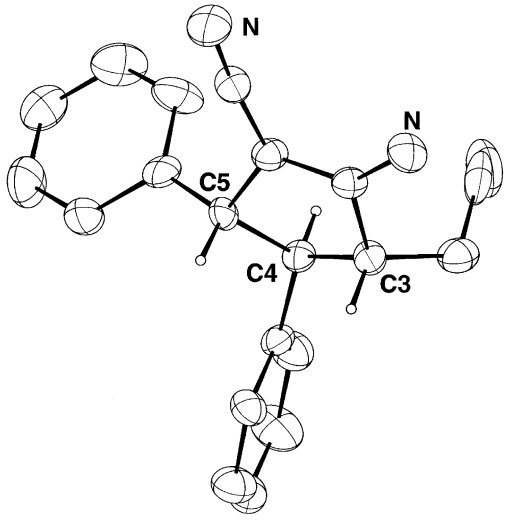
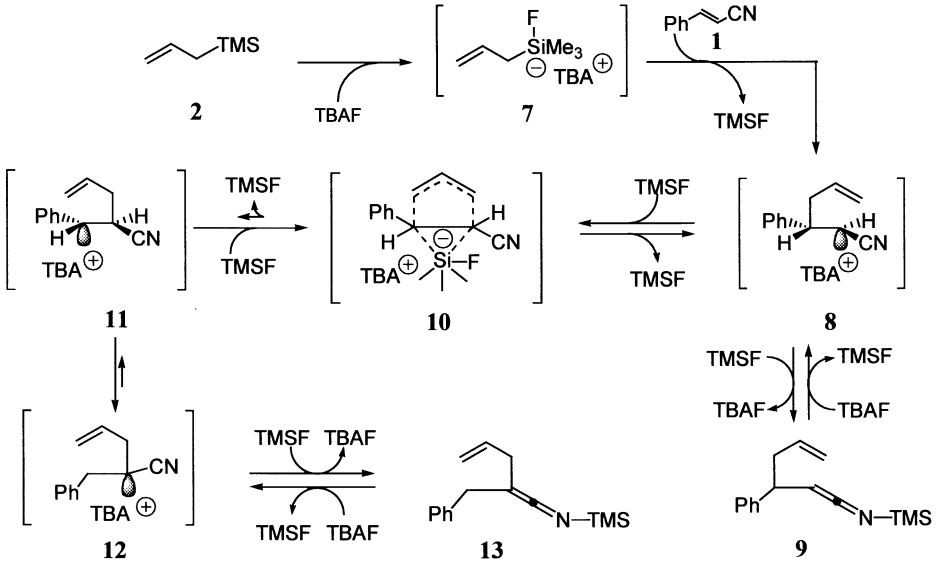


Figure 1. ORTEP view of **5** with labeled heteroatoms and stereogenic atoms. Thermal ellipsoids are scaled to 30% probability level. Hydrogen atoms shown are drawn to an arbitrary scale.

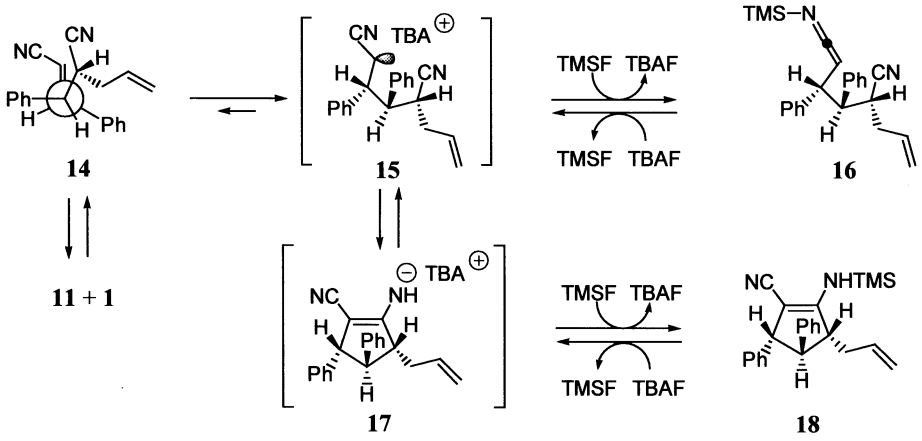
Structure of the second by-product was elucidated to be (2*R**,3*S**,4*R**)-2-allyl-3,4-diphenyl-hexanedinitrile (**6**)[5] on the basis of molecular ion peak at m/z 300 in mass spectroscopy, of IR spectrum and of ^1H and ^{13}C NMR data including 2D-experiments. The depicted relative configuration of the three stereogenic centers, although not definitively established, rests on mechanistic considerations assuming that dinitrile **6** and enaminonitrile **5** both derived from the parent carbanion **15** (vide infra, Scheme 3).

Both by-products **5** and **6** arising from a further *intermolecular* nucleophilic addition (see Schemes 2 and 3), we reasoned that this undesirable side reaction may be minimized by simple lowering of the concentration of reactants **1** and **2**. To support this hypothesis, the above Majetich protocol[2] was repeated, having diluted *10 times* the reagents in DMF and having added *all at once* the solution of **2** and HMPA to the solution of **1** and TBAF. In such conditions, the main products isolated were found to be the expected 1,4-adduct **3**[2] and its regioisomer **4** as ca. 2:1 mixture in 90% combined yield, along with a small amount of by-product **5** (ca. 5% yield). All attempts at separating the components of mixture (**3**+**4**),[6] employing standard chromatographic methods (TLC, GC, HPLC) proved to be unsuccessful. However, the minor component of this mixture was authenticated as the 'abnormal Sakurai adduct' (2-benzyl-4-pentenenitrile, **4**, resulting from the formal *1,3-addition* of allylsilane **2** to nitrile **1**), by comparison of its ^1H and ^{13}C NMR data with those reported in the literature.[7]

Formation of products **3**, **4**, **5** and **6** can be rationalized, invoking the fluoride-triggered autocatalytic mechanism depicted in Schemes 2 and 3. As previously postulated,[2] the process is probably initiated by the nucleophilic pentacoordinate silicon complex **7** issuing from the condensation of TBAF with allylsilane **2**. 1,4-Addition of **7** to nitrile **1** next delivers anion **8**, the



Scheme 2.



Scheme 3.

trapping of which by TMSF furnishing the neutral *N*-silylated species **9**. Anion **8** is also capable of equilibrating with regioisomer **12**, through the benzylic anion **11**. This rearrangement first involves a 1,2-anion shift and concomitant sigmatropic transposition of the allyl group, possibly via the nonclassical silicon complex **10**, leading to transient benzylic ion **11**. The latter next stabilizes by 1,2-[*H*] transfer, giving rise to translocated anion **12** which is trapped with TMSF to afford the *N*-silylated derivative **13** (Scheme 2).

The two-step anionic rearrangement [**8**→**12**] deserves comment. The first step [**8**→**11**] being clearly thermodynamically disfavored (compare the pK_a values of acetonitrile and toluene, 31 and ca. 43, respectively), the process requires a high energy of activation. However, since carbanions **8** and **12** are both stabilized by an α-nitrile group, one may infer that they are close in energy. Therefore, provided that a stationary state is attained, *a close population of regioisomeric anions **8** and **12** is expected*. On the other hand, it should be noted that the benzylic anion **11**, being less stabilized (and less populated) than its congeners **8** and **12** is correlatively much more reactive, and therefore can play the role of favorite nucleophilic partner in a subsequent Michael addition. In fact, when the reactants are present at a relatively high concentration level a competing Michael-type addition of benzylic anion **11** to a second molecule of cinnamonitrile (**1**) now occurs, leading to carbanion **15** precursor of silylated compound **16**. It is noteworthy that, although primarily governed by the concentration of reagents, this Michael addition is thermodynamically favored, the developing carbanion **15** being much more stabilized than its progenitor **11**. Alternatively, anion **15** can undergo a Thorpe–Ziegler annulation,[8] furnishing **17** precursor of **18**. Further protiodesilylation during workup of the *N*-silylated compounds **9**, **13**, **18** and **16** finally delivers products **3**, **4**, **5** and **6**, respectively (Scheme 3).

The remarkable complete stereocontrol of the three stereogenic centers present in by-products **5** and **6** can be interpreted, assuming first that the transient benzylic anion retains the configuration shown in formula **11** (one enantiomer is arbitrarily represented), reflecting on the one hand the *trans* stereochemistry of starting nitrile **1**, and on the other hand the *anti* relationship between the migrating allyl appendage and the bridged silicon ion in putative intermediate **10**. The stereochemical course of the subsequent Michael addition of benzylic anion **11** to α,β-ethylenic nitrile **1**, furnishing the fully stereocontrolled pivotal ion **15** can in turn be rationalized, invoking approach **14**. The reason for the orientation of the reactants in this approach presumably lies in a conjunction of two factors: the positioning of the nitrile ends close to each other, a prerequisite of the subsequent Thorpe–Ziegler ring closure, and the preferential attack of anion **11** on the *Re* π-face of electrophilic partner **1**, thus minimizing the Ph–Ph repulsive interaction.

To conclude, we have demonstrated that under standard operating conditions the fluoride-mediated condensation of cinnamonitrile (**1**) with allyltrimethylsilane (**2**) furnished essentially a mixture of by-products **5** and **6**, resulting from sequential 'abnormal Sakurai'–Michael–Thorpe Ziegler and 'abnormal Sakurai'–Michael side reactions. Although these undesirable processes could be almost completely suppressed by an appropriate dilution of the reaction medium, the synthesis of the desired Sakurai adduct **3** was found now to be thwarted by the concomitant formation of a significant amount of the 'abnormal regioisomer' **4**.

Acknowledgements

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4. Enaminonitrile **5**: White solid; mp 58–59°C (AcOEt/pentane); $R_f=0.21$ (silica gel, 20% AcOEt in cyclohexane); IR (neat, cm^{-1}) ν: 3480, 3363, 2185, 1639, 1597; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.27–2.34 (m, 2H), 2.84 (t, $J=8.3$ Hz, 1H), 3.06 (m, 1H), 4.01 (d, $J=8.3$ Hz, 1H), 4.85 (bs, 2H), 5.14 (d, $J=10.2$ Hz, 1H), 5.19 (d, $J=13.7$ Hz, 1H), 5.72–5.86 (m, 1H), 7.03–7.15 (m, 4H), 7.19–7.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 163.3 (C), 142.2 (C), 141.4 (C), 135.1 (CH), 128.4 (2CH), 128.2 (2CH), 127.8 (2CH), 127.1 (2CH), 126.8 (CH), 126.7 (CH), 118.2 (C), 118.1 (CH_2), 77.1 (C), 59.2 (CH), 56.4 (CH), 51.0 (CH), 35.3 (CH_2); MS (EI, −70.0 V) m/z (rel. intensity): 301 (M+1, 14), 300 (*M*, 51), 271 (30), 259 (100), 256 (63). Anal. calcd C, 83.96; H, 6.71; N, 9.33. Found: C, 83.81; H, 6.70; N, 9.30%.
5. Dinitrile **6**: White solid; mp 159–160°C; $R_f=0.47$ (silica gel, 20% AcOEt in cyclohexane); IR (neat, cm^{-1}) ν: 2243; ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.98 (t, $J=7.7$ Hz, 2H), 2.36 (d, $J=5.6$ Hz, 1H), 2.39 (d, $J=2.7$ Hz, 1H), 2.56 (dt, $J=7.7$, 4.2 Hz, 1H), 3.18 (dd, $J=12.0$, 4.2 Hz, 1H), 3.58 (ddd, $J=7.2$, 4.6, 4.2 Hz, 1H), 4.98 (dq, $J=17.0$, 1.5 Hz, 1H), 5.08 (dq, $J=10.3$, 1.5 Hz, 1H), 5.54 (ddt, $J=17.0$, 10.3, 6.9 Hz, 1H), 7.20–7.60 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 139.0 (C), 136.4 (C), 132.8 (CH), 129.7 (4CH), 129.5 (CH), 128.7 (2CH), 128.6 (2CH), 127.6 (CH), 119.0 (2C), 117.7 (CH_2), 49.8 (CH), 45.4 (CH), 34.9 (CH_2), 34.6 (CH), 23.8 (CH_2); MS (ESI, +32.0 V, MeOH+$HCOONH_4$) m/z (rel. intensity): 323 (M+Na^+, 67), 318 (M+NH_4^+, 100), 301 (M+H^+, 32).
6. Mixture of regioisomers (**3**+**4**): colorless oil; $R_f=0.62$ (silica gel, 20% AcOEt in cyclohexane); selected pertinent ^{13}C NMR data ($CDCl_3$, 50 MHz) δ: **3**: 23.8 (CH_2), 39.1 (CH_2), 41.6 (CH); **4**: 33.4 (CH), 35.6 (CH_2), 37.6 (CH_2).
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