

Diazo Transfer Reagent 2-Azido-4,6-Dimethoxy-1,3,5-Triazine (ADT) Displays Highly Exothermic Decomposition Comparable to Tosyl Azide

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Supporting Information Placeholder

ABSTRACT: 2-Azido-4,6-dimethoxy-1,3,5-triazine (ADT) was reported recently as a new ‘intrinsically safe’ diazo transfer reagent. This assessment was based on Differential Scanning Calorimetry (DSC) data indicating that ADT exhibits endothermic decomposition. We present DSC data on ADT that show exothermic decomposition with an initiation temperature (T_{init}) of 159 °C and an enthalpy of decomposition (ΔH_D) of -1135 J g^{-1} (-207 kJ mol^{-1}). We conclude that ADT is potentially explosive and must be treated with caution, being of comparable exothermic magnitude to tosyl azide (TsN_3). A maximum recommended process temperature for ADT is 55 °C.

Diazo transfer reagents effect the transfer of N_2 to activated methylene substrates and amines to generate diazo and azide compounds respectively. Although a range of organoazide diazo transfer reagents exist (Figure 1), sulfonyl azides are the most widely used.¹ Sulfonyl azides are, however, highly energetic due to the thermodynamically favourable formation of gaseous decomposition products, and some are reported to be impact sensitive and potentially explosive.^{2,3} Improving the safety profile of diazo transfer reagents has been a key driver in this field since the initial use of tosyl azide (TsN_3) over 50 years ago.⁴

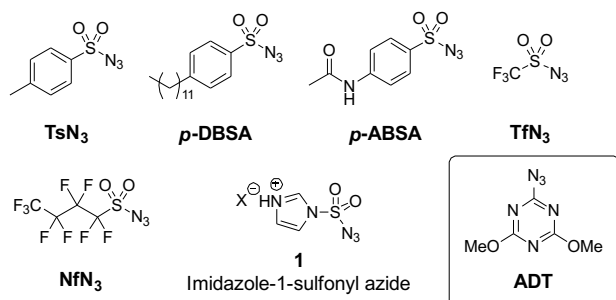


Figure 1. Selected Diazo Transfer Reagents

p-Dodecylbenzenesulfonyl azide (*p*-DBSA) was introduced as a safer alternative to TsN_3 owing to its lower enthalpy of decomposition (ΔH_D), reduced impact sensitivity and higher thermal stability.² More recently, *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) has found extensive use as a diazo transfer reagent. *p*-ABSA has a similar safety profile to *p*-DBSA, however the greater polarity differences between *p*-ABSA and typical activated methylene substrates facilitate product separation.⁵ A polystyrene-supported benzenesulfonyl azide (PSS-BSA) has also been proposed as a safer reagent but suffers from high cost and poor atom economy.⁶

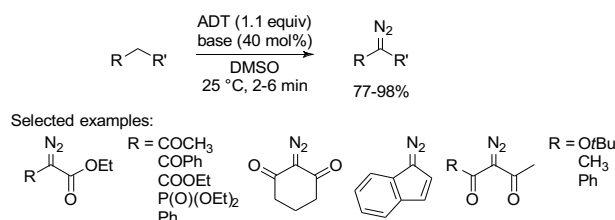
As a replacement for the more reactive but sensitive and explosive triflyl azide (TfN_3), nonafluorobutanesulfonyl azide (NfN_3) has been demonstrated to be insensitive, less exothermic and can be isolated and stored while still maintaining the high reactivity.⁷ Imidazole-1-sulfonyl azide **1** HCl salts were proposed to be safe until samples spontaneously exploded,⁸ highlighting the need for rigorous safety investigations for novel azide reagents. Later investigations discovered that the H_2SO_4 salt was insensitive and safer to handle, however its preparation still required isolation of the highly impact sensitive imidazole-1-sulfonyl azide.⁹ Recently, an improved route to **1**· H_2SO_4 that circumvents the isolation of imidazole-1-sulfonyl azide has been reported.¹⁰ Thermal analysis data for these selected diazo transfer reagents is given in Table 1.¹¹ Less hazardous reagents would be highly attractive for all applications as substitution is an effective chemical hazard control measure.¹²

Table 1. Diazo Transfer Reagents with Improved Safety Profile¹¹

entry	diazo transfer reagent	T _{init} (°C)	T _{onset} (°C)	ΔH _D (J g ⁻¹)	ΔH _D (kJ mol ⁻¹)	ref
1	TsN ₃	120	156 ^a	-1696	-334	2
2	<i>p</i> -DBSA	151		-703	-247	2
3	<i>p</i> -ABSA	120	155 ^b	-720	-173	5
4	PSS-BSA	130	166	-275	-183	6
5	NfN ₃	120 ^c	141	-419	-136	7c

^a from reference 13. ^b from reference 14. ^c from reference 15.

Ma recently reported the novel azido triazine diazo transfer reagent, 2-azido-4,6-dimethoxy-1,3,5-triazine (ADT). This was shown to be effective in the transfer of N₂ to a variety of activated methylene positions (Figure 1 and Scheme 1).¹⁶ The reaction was reported to proceed rapidly in DMSO using various bases, and achieved excellent yields of diazo compounds with a variety of substrates. We observed similarly successful results with this reagent.

Scheme 1. Diazo Transfer Reaction with ADT

The report was particularly notable since the diazo transfer reagent, ADT, was described as being intrinsically safe: insensitive to impact and exhibiting an endothermic decomposition ($\Delta H_D = +30 \text{ kJ mol}^{-1}$, see Figure 2). Such properties avoid the risk of a thermal runaway. The endothermic decomposition was determined by Differential Scanning Calorimetry (DSC), which measures the energy difference between a sample crucible and an inert reference. DSC is a valuable screening tool in process safety to investigate thermal hazards. The original work also demonstrated ADT to be insensitive to impact and friction using standard tests described by the UN Recommendations on the Transport of Dangerous Goods.¹⁷

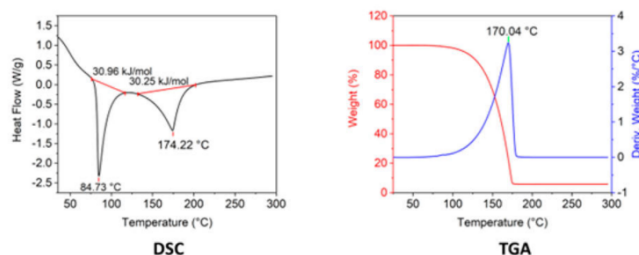
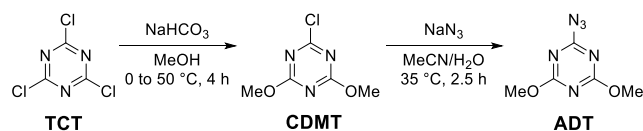


Figure 2. Reported DSC and TGA plots for ADT from Ma. Reproduced from Xie, S.; Yan, Z.; Li, Y.; Song, Q.; Ma, M. *J. Org. Chem.* 2018, 83, 10916–10921. Copyright 2019 American Chemical Society.

As part of a broader study on energetic diazo transfer reagents and diazo compounds, and given the interest to the academic and industrial communities of a reagent considered safe, we examined ADT. Here we report our findings from DSC and TGA-MS experiments and conclude, contrary to Ma's report, that ADT exhibits exothermic decomposition of a magnitude that may be predicted

to exhibit explosive propagation. We also present a rationale for the differing conclusions drawn by Ma from their data.

ADT was prepared in one step from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) or in two steps from 2,4,6-trichloro-1,3,5-triazine (TCT) as reported by Ma (Scheme 2).¹⁶ Both the intermediate CDMT and precursor TCT are commercially available peptide coupling reagents. DSC analysis on TCT and CDMT was recently reported by Pfizer and neither was considered to be potentially impact sensitive or explosive (For TCT: T_{init} = 360 °C, $\Delta H_D = -36 \text{ J g}^{-1}$; For CDMT: T_{init} = 161 °C and $\Delta H_D = -513 \text{ J g}^{-1}$).¹⁸

Scheme 2. Synthesis of ADT

Ma reported thermal analysis of ADT by Thermogravimetric Analysis (TGA) and DSC (Figure 2; Table 2 entry 1).^{16,19} For both techniques a 2.5 mg sample was heated at 5 °C min⁻¹ but further details of the procedure were not provided.

In our study, ADT was analysed by DSC using 5 mg of sample, weighed into a stainless steel high-pressure crucible, sealed, and analysed with a temperature ramp of 5 °C min⁻¹ (for more detail, see Experimental Section). The results for initiation temperature (T_{init}), extrapolated onset temperature (T_{onset}) and enthalpy of decomposition (ΔH_D) were measured for two samples and averaged. This analysis was repeated on a different machine at GlaxoSmithKline (GSK) using a slightly different method involving gold-plated high-pressure crucibles and a 2 °C min⁻¹ temperature ramp. Table 2 gives the raw and averaged data from both sets of experiments compared to those obtained by Ma.

A representative DSC plot for ADT is given in Figure 3 for comparison with the originally reported plot in Figure 2. The melting point occurs at a similar temperature and then a significant exotherm of -1135 J g^{-1} is observed. This is in clear contrast with the results from Ma.

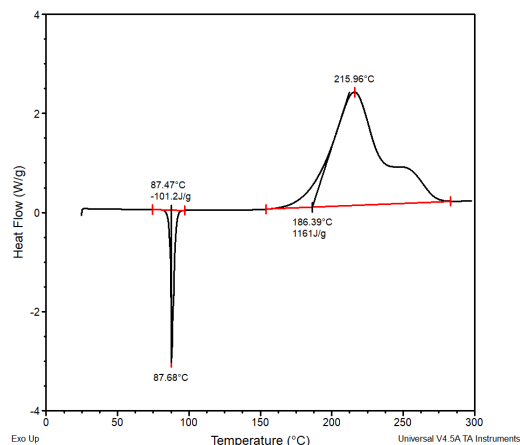


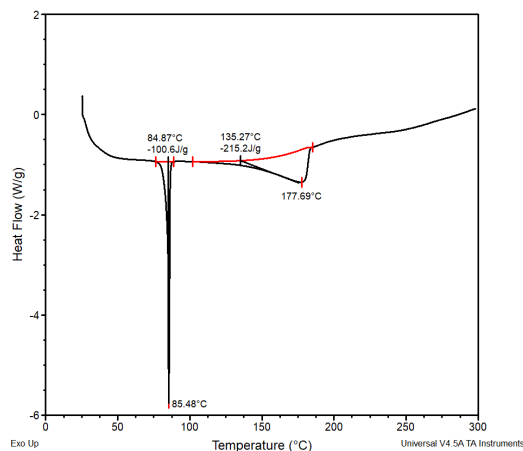
Figure 3. DSC Plot of ADT (Table 2, Entry 3)

Table 2. DSC data of ADT and Other Diazo Transfer Reagents¹¹

entry	DSC Result	melting point (T_{peak} , °C)	T_{init} (°C)	T_{onset} (°C)	T_{peak} (°C)	ΔH_D (J g ⁻¹)	ΔH_D (kJ mol ⁻¹)
1	Ma <i>et al</i>	84.73	approx 130 ^a	approx. 150 ^a	174	+166 ^b	+30.3
2	ADT result 1 ^c	87.84	158	187	218	-1103	-201
3	ADT result 2 ^c	87.68	159	187	216	-1161	-211
4	ADT avg	87.76	159	187	217	-1135	-207
5	GSK ADT result 1 ^d	87.5	142	178	206	-1248	-227
6	GSK ADT result 2 ^d	86.5	144	178	205	-1231	-224
7	GSK ADT avg	87.0	143	178	206	-1240	-226
8	ADT open crucible ^e	85.5	110	135	178	+213	+39
9	tosyl azide result 1 ^c		131	158	186	-1088	-215
10	tosyl azide result 2 ^c		125	158	186	-1025	-202
11	tosyl azide avg		128	158	186	-1057	-209

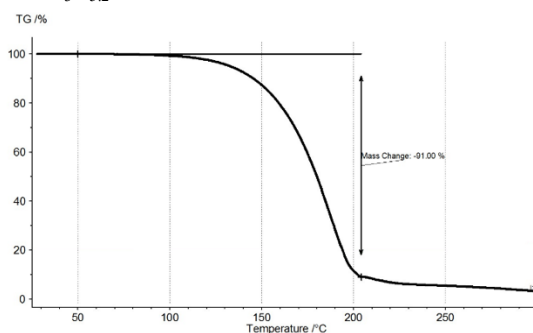
^a Estimated from DSC plot. ^b Calculated from reported ΔH_D kJ mol⁻¹ value. ^c Using DSC method A (see experimental). ^d Using DSC method B (lower measured temperatures are due to a slower scan rate). ^e Using DSC method C with unsealed crucible. See Figure 4 for plot.

The most likely reason for the endothermic transition observed in the previous report is gas loss from the sample, occurring during decomposition.²⁰ As gaseous products from decomposition escape the sample crucible they remove heat from the system, resulting in detection of an endotherm. This hypothesis was tested by performing DSC analysis on a sample of ADT in an open crucible. The resulting plot was found to closely match the DSC plot reported by Ma (Figure 4 and Table 2, Entry 5). Here the endothermic gas loss completely obscured the exothermic decomposition (1135 J g⁻¹). Indeed, the magnitude of exotherm upon decomposition is similar to that observed for tosyl azide using the same DSC method (Table 2 Entries 9-11).² Since tosyl azide is known to be explosive,^{2,21} ADT therefore could also present a potential explosion hazard.

**Figure 4. DSC Plot of ADT with unsealed crucible**

TGA coupled to Evolved Gas Mass Spectrometry (EGMS) was used to investigate the decomposition products. Using a 5 °C min⁻¹ heating rate, the TGA plot in Figure 5 shows mass loss commencing as early as 85 °C, significant mass loss occurring from 150-200 °C (T_{onset} 158.8 °C, the inflection point analogous to T_{peak} at 182.7 °C and ending at 200.1 °C) and leaving a residue of 3.23% of the original mass at 300 °C. Approx 90% of the mass of ADT is converted to gas by 205 °C; it is this particularly high proportion of gas loss that gives rise to an endotherm of sufficient

magnitude to fully obscure the significant exotherm. From the EGMS trace, the following mass ions were detected above baseline levels, in abundance order with assignments: 28 (N₂, normalised to 100% intensity), 14 (N, 7.7%), 40 (NCN, 2.2%), 29 (¹⁵N≡N, 0.76%), and trace mass ions (<0.1% relative intensity) 27 (HCN), 20, 15 (¹⁵N or CH₃), 18 (H₂O), 12 (C), 30 (NO), 36, 44 (CO₂), 54, 70. A previously reported analysis of the pyrolysis products of 2,4,6-triazido-1,3,5-triazine found only N₂ gas and polymeric C₃N_{5.2} residue.²²

**Figure 5. TGA plot of ADT.**

Application of the Yoshida correlation²³ allows the prediction of explosive propagation in material (eq 1). From this equation, which correlates the T_{onset} and Q (the energy released upon decomposition, in cal g⁻¹) with results from known explosive, borderline explosive and non-explosive materials. An output with a positive value predicts the material can detonate (propagating an explosive shockwave). A negative value would predict the material, though exothermic, is not capable of explosive decomposition.

$$EP = \log_{10}(Q) - 0.38[\log_{10}(T_{onset} - 25)] - 1.67 \quad (1)$$

(where Q is the energy released upon decomposition in cal g⁻¹)

There is also a modified form used by Pfizer which is more conservative, reducing the Q term by 25% and using T_{init} (eq 2).¹⁸

$$EP = \log_{10}(Q) - 0.285[\log_{10}(T_{init} - 25)] - 1.67 \quad (2)$$

Applying the average values obtained from the DSC of ADT gave the outputs given in Table 3. The Yoshida correlation is close to the prediction threshold and the more conservative Pfizer-

modified correlation predicts explosive propagation. It is therefore highly recommended that further explosivity screening with either a specially modified Accelerating Rate Calorimeter (ARC)²⁴ or definitive UN Class 1 testing¹⁷ is conducted before using ADT in a large scale process. Note that even if a material cannot propagate explosive detonation, it may still cause explosive rupture of a vessel upon decomposition due to rapid gas evolution.

Table 3. Application of Yoshida EP Correlation to DSC results

entry	DSC result	Yoshida EP	Pfizer-modified EP
1	ADT avg ^a	-0.08	0.13
2	GSK ADT avg ^b	-0.03	0.18
3	tosyl azide avg ^a	-0.07	0.13

^a Using DSC Method A. ^b Using DSC Method B.

From a process safety perspective an exotherm of this magnitude is cause for concern. Though the compound was demonstrated to be insensitive to impact, there is still potential for thermally-initiated decomposition. Process Safety at GSK use a formula to determine a maximum recommended safe process temperature, defined by Stoessel, given in eq 3.²⁵

$$T_{D24} = 0.7 \times T_{init} - 46 \quad (3)$$

The recommendation is based on zero-order Arrhenius kinetics of a runaway thermal decomposition reaction, where T_{D24} is the temperature at which the Time to Maximum Rate under adiabatic conditions (TMR_{ad}) is 24 h and there is therefore minimal risk of triggering runaway decomposition. T_{init} is used as it represents an approx 0.01 W g⁻¹ exothermic baseline shift as detected in the DSC experiment.

Using the lowest averaged T_{init} obtained for ADT (measured with the 2 °C min⁻¹ temperature ramp), the maximum recommended safe process temperature is 55 °C, rounded to the nearest 5 °C. Applying the same process for tosyl azide gives a maximum recommended safe process temperature of 45 °C.²⁶ Additionally, adequate thermal control must be in place to prevent overheating and consideration must also be given to evolved gas in a potential thermal runaway scenario. In any case, it is advisable to minimise the risk profile of a process firstly by selection of a less hazardous reagent if available.

In summary, ADT was recently developed as an effective diazo transfer reagent to form diazo compounds with activated methylenes using an inorganic base in DMSO. However, it was also reported as being ‘intrinsically safe’ due to an endothermic decomposition. We have demonstrated that the DSC result previously presented does not accurately represent the exothermic decomposition of ADT. Analysis of the decomposition of compounds where gas evolution may occur should be performed in sealed crucibles capable of containing the pressure generated to minimise the possibility of misleading results. Our data shows ADT has a highly exothermic decomposition where T_{init} is 159 °C, T_{onset} is 187 °C and ΔH_D is -1135 J g⁻¹ (-207 kJ mol⁻¹). Although ADT has a higher initiation and onset temperature than tosyl azide and has been demonstrated by Ma to be insensitive to impact and friction, care must be taken to avoid decomposition of ADT during a reaction or other processing of this compound (e.g. drying, recrystallizing), as the large exotherm and evolved gas present a similar explosion hazard. A maximum process temperature of 55 °C is therefore recommended based upon DSC data alone. However, it should be recognised that for materials that exhibit such a hazardous decomposition profile, further study is strongly rec-

ommended, for example by using an adiabatic technique such as Accelerating Rate Calorimetry.

EXPERIMENTAL SECTION

DSC Experimental Terminology: T_{init} is defined by the temperature at which the heat flow is measured to be > 0.01 W g⁻¹ from the baseline. T_{onset} is defined by the intersection of the extrapolated maximum peak slope and the baseline. ΔH_D is obtained by integration of the peak. Averaged DSC results reported where individual results have <1% difference from the average for T_{init} and T_{onset} and <5% difference from the average for ΔH_D .

DSC Method A: DSC analysis was performed using a TA Instruments Q2000 DSC with LNCS. Approx 5 mg was weighed into a reusable PerkinElmer B0182901 stainless steel high-pressure crucible with disposable gold-plated copper seal rated to 150 bar and sealed under air with the appropriate B0182864 sealing tool. After equilibrating at 25 °C, samples were heated at 5 °C min⁻¹. Data analysis was conducted using TA Instruments Universal Analysis 2000 software version 4.5.0.5.

DSC Method B: DSC analysis was performed using a Mettler Toledo DSC 823e. Approx 5 mg was weighed into a Mettler Toledo ME-26731 gold-plated 40 µl high-pressure crucible with seal insert and lid rated to 150 bar, and sealed under air with the appropriate sealing press. After equilibrating at 25 °C, samples were heated at 2 °C min⁻¹. Data analysis was conducted using Mettler Toledo STARE software version 12.00 build 5342.

DSC Method C (open crucible): DSC analysis was performed using a TA Instruments Q2000 DSC with LNCS. Approx 2 mg was weighed into TA Instruments 901683.901 Tzero aluminium crucible and 901684.901 Tzero hermetic lid, sealed under air with the appropriate 901600.901 Tzero sample press and 901608.904 Tzero hermetic die set and then pierced with a needle to leave two holes of approx 1 mm diameter. After equilibrating at 25 °C, samples were heated at 5 °C min⁻¹. Data analysis was conducted using TA Instruments Universal Analysis 2000 software version 4.5.0.5.

TGA-MS Experimental Method: TGA-MS was performed on a Netzsch TG209 F1 Libra TGA and Netzsch QMS 403 D Aeolos (cross beam EI) EGMS. Approx 20 mg was weighed into an open Al₂O₃ crucible. A temperature ramp of 5 °C min⁻¹ and purge gas flow of 40 ml min⁻¹ N₂ was used. For the EGMS, a Fast SCB scan of mass range 10-70 was used. A plot of all mass ions was obtained and filtered to display those that showed a significant increase upon decomposition of ADT, determined by the TGA. The baseline was determined by the average of mass ion intensity from 10 EGMS cycles from 8.32 min (67 °C) to 10.45 min (77 °C) and the decomposition gases determined by subtraction of the baseline for each mass ion from the average of 3 EGMS cycles from 32.88 min (189 °C) to 33.30 min (192 °C) for that mass ion. EGMS traces and full data can be found in the SI.

General Experimental Methods. All non-aqueous reactions were run under an inert atmosphere (nitrogen) with flame-dried glassware using standard techniques. Anhydrous solvents were obtained by filtration through drying columns (MeCN) or used as supplied (MeOH, DMSO). Commercial reagents were used as supplied. Flash column chromatography was performed using 230-400 mesh silica with the indicated solvent system. Analytical thin-layer chromatography was performed on precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), or aq potassium permanganate stain. Infrared spectra (FTIR) were recorded in reciprocal centimeters (cm⁻¹) using a FTIR ATR spectrometer. Nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer. Chemical shifts for ¹H NMR spectra are recorded in

parts per million with the residual protic solvent resonance as the internal standard (chloroform: 7.27 ppm). Data were reported as follows: chemical shift (multiplicity, integration). ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million with the solvent resonance as the internal standard ($^{13}\text{CDCl}_3$: 77.0 ppm).

Synthetic Procedures:

ADT was prepared according to the report from Ma *et al.*¹⁶ CDMT is commercially available.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

DSC plots of ADT, TGA plot of ADT, EGMS traces, synthetic details and ^1H and ^{13}C NMR spectra for ADT. (PDF)

All characterization data for synthesized compounds, raw DSC and TGA-EGMS data for ADT can be found at <https://doi.org/10.14469/hpc/4946>.

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Notes

The authors declare no competing financial interests.

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(19) In a previous report without experimental details, the decomposition of ADT was found to occur at 195 °C. Kayama, R.; Hasunuma, S.; Sekiguchi, S.; Matsui, K. The Thermal Reactions of Azido-1,3,5-triazines. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2825–2829.

(20) An alternative explanation could be that ADT evaporates from the open crucible before decomposition. However, due to the high melting point and reported TGA of the decomposition of similar compound 2,4,6-triazido-1,3,5-triazine, this seems less likely (See reference 22).

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(23) Yoshida, T.; Yoshizawa, F.; Itoh, M.; Matsunaga, T.; Watanabe, M. Prediction of Fire and Explosion Hazard for Reactive Chemicals (I): Estimation of Explosive Properties of Self-Reactive Chemicals from SC-DSC Data. *Kogyo Kagaku.* **1987**, *48*, 311–316 (British library translation available). A salient application of Yoshida's correlations can be found in the Pfizer peptide coupling work (See reference 18).

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(26) This maximum recommended process temperature was determined using T_{init} obtained from DSC data with a $5\text{ }^{\circ}\text{C min}^{-1}$ temperature ramp.

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