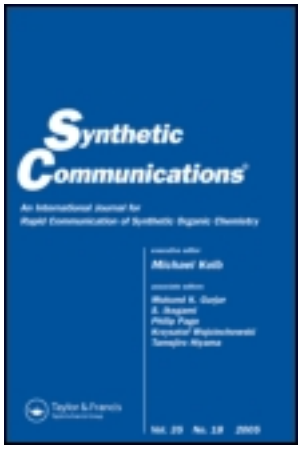

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Temperature-Gradient-Directed NMR Monitoring of a [3 + 3]-Cyclocondensation Reaction Between Alkynone and Ethyl 2-Amino-1H-indole-3-carboxylate Toward the Synthesis of Pyrimido[1,2-a]indole Catalyzed by Cs_2CO_3

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TEMPERATURE-GRADIENT-DIRECTED NMR MONITORING OF A [3 + 3]-CYCLOCONDENSATION REACTION BETWEEN ALKYNONE AND ETHYL 2-AMINO-1*H*-INDOLE-3-CARBOXYLATE TOWARD THE SYNTHESIS OF PYRIMIDO[1,2-*a*]INDOLE CATALYZED BY Cs_2CO_3

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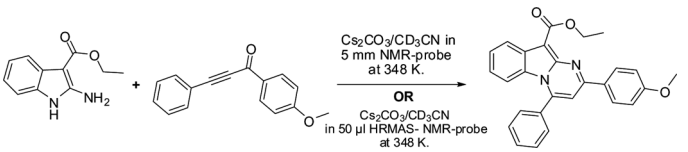
GRAPHICAL ABSTRACT



Abstract *We describe a NMR strategy to resolve temperature-gradient-monitored real-time chemical reaction involving a [3 + 3]-cyclocondensation reaction between alkynone and ethyl 2-amino-1*H*-indole-3-carboxylate toward the synthesis of pyrimido[1,2-*a*]indole catalyzed by Cs_2CO_3. The in situ NMR study clearly indicates that the reactant undergoes [3 + 3]-cyclocondensation reaction through a concerted mechanism, resulting in the product formation. The detailed NMR spectroscopic data led to the optimization of the reaction conditions and quantitative analysis of the product accurately and efficiently.*

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Keywords Alkynone; cyclocondensation; heterogenous catalyst; ^{1}H NMR; HR-MAS; magic angle; nucleophile

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INTRODUCTION

Nuclear magnetic resonance (NMR) has evolved into a nondestructive and enlightening technique in different fields of natural sciences[1] such as biochemistry,[2] biology,[3] medicine,[4] and all branches of chemistry.[5] The beauty of NMR over other spectroscopic techniques is its noninvasive/nonoptical sampling and the wide variety of experiments made possible by an almost unlimited choice of radio-frequency pulse sequences that may be used for observing nuclear spin.[6] NMR spectroscopy, being noninvasive in nature, is one of the best techniques for monitoring chemical and enzymatic reactions.[7] At high magnetic fields, there is usually enough frequency resolution to follow the fate of each molecular species, even if they have closely related or isomeric structures.[8] Moreover, the linear correlation between resonance intensity and molar quantity of each component of the reaction makes measuring the time course of enzyme-catalyzed conversions relatively simple.[9] The major problem associated with the use of solution-phase NMR technique for real-time heterogeneous reactions is the peak broadening. The chemical shift anisotropy is created during the experiment by the presence of solid catalytic material.

In nuclear magnetic resonance, magic angle spinning (MAS) is a technique often used to perform experiments in solid-state NMR spectroscopy.[10] High-resolution–magic angle spinning nuclear magnetic resonance (HR-MAS NMR) allows the application of solution-state NMR experiments to samples that are not fully soluble and contain solids.[11] It allows the analysis of materials that swell, become partially soluble, or form true solutions in a solvent even when some solids are still present.[12] In an HR-MAS experiment, a heterogeneous or multiphase sample is spun at a high speed (typically 3–5 kHz) around an axis oriented at an angle of 54.7° magic angle with respect to the direction of the static magnetic field. Because of the presence of solid heterogeneous catalyst Cs_2CO_3, this reaction optimization is also carried out by HR-MAS NMR.

Keeping this in our mind, and because of continuation of our interest in the synthesis of indole-based polycycles of biological interest,[13] we herein report monitoring/synthesis of a [3 + 3]-cyclocondensation reaction by temperature gradient NMR measurements in an NMR probe in solution state as well as in HR-MAS mode. To the best of our knowledge, such a study has not been performed. For this purpose, bifunctional nucleophile (N^aH and N^bH$_2$), 2-amino-1*H*-indole-3-carboxylate **1**, and bifuctional 3-carbon building block alkynones **2** catalyzed by solid Cs_2CO_3 were selected to furnish a pyrimidine ring annulated to the indole, a privilege class molecule. In this study, solid heterogeneous catalyst Cs_2CO_3 does not hamper the analysis in liquid-phase NMR even with temperature and spinning. The material does not swell and the catalyst remains below the RF coil. NMR of liquid is easier because an internal molecular motion already eliminates effects of the chemical shift anisotropy and magnetic dipole–dipole interactions.

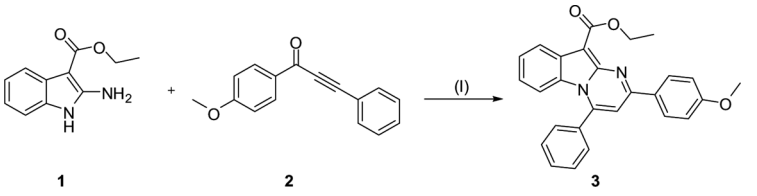
RESULTS AND DISCUSSION

The reaction was initially standardized by refluxing the ethyl 2-amino-1*H*-indole-3-carboxylates **1** (100 mg, 0.423 mmol) and 1-(4-methoxyphenyl)-3-phenyl-prop-2-yn-1-one **2** (86 mg, 0.423 mmol) in the presence of Cs_2CO_3 as the base

(210 mg, 0.635 mmol) in 5 ml of acetonitrile. It showed complete conversion of the starting material on thin-layer chromatography (TLC) after 6 h (Scheme 1). The crude reaction mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure in vacuo. The crude reaction mixture was purified by column chromatography on 60 to 120-mesh silica using EtOAc/hexane (1:19) as eluent to afford ethyl 2-(4-methoxyphenyl)-4-phenyl-pyrimido[1, 2-a]-indole-10-carboxylate **3** in 80% quantitative isolated yield and 93% purity based on high-performance liquid chromatography (HPLC). No traces of the starting material or any other by products were detected. The isolated compound was characterized by using NMR spectroscopy in $CDCl_3$ and details are given in the Supplemental material, available online.

The reaction was carried out in CH_3CN at reflux in the conventional method, so in the NMR tube CD_3CN was used as reaction medium. On the basis of NMR spectra in CD_3CN of two starting materials and the final product obtained after purification, we conclude that the disappearance of signals N^aH and N^bH_2 at 8.92 and 6.03 ppm in 2-amino-1*H*-indole-3-carboxylates **1**, the slight shifting of two doublets of *p*-methoxy substituted aryl ring of 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one **2** towards downfield from 7.08, 8.18 to 7.10, 8.36 respectively, and the appearance of signal at 7.29 singlet of the pyrimidine ring clearly indicate the formation of 2-(4-methoxyphenyl)-4-phenyl-pyrimido[1,2-a]indole-10-carboxylate **3**.[14]

To get an insight into the mechanism of this pyrimido[1,2-a]indole formation, the reaction was monitored by real-time NMR measurements in an NMR probe using 600 µl of the total reaction mixture under stoichiometric conditions (0.021 mmol of **1**, 0.021 mmol **2**, and 0.0318 mmol of base) in deuterated acetonitrile (CD_3CN). The recording of the NMR spectra were carried out as soon as the shimming and temperature of the mixture were maintained. From NMR studies it was found that no reaction occurred when where **1** and **2** mixed together in the absence of a base. The starting materials were retained as such even after increasing the temperature from 303 to 328 K (Fig. 1). Then, in a NMR tube, Cs_2CO_3 was added to a solution of **1** and **2** in deuterated acetonitrile, and the reaction started slowly as the NMR peaks of starting materials were diminished while the new peaks started to form in trace amounts at 303 K. The N^aH and N^bH_2 of **1** disappeared immediately and appearance of product **3** started slowly without the formation of other intermediates at different temperature ranges. Monitoring of the reaction continued and we observed the complete conversion of starting materials **1** and **2** into



Scheme 1. Synthesis of 2-(4-methoxyphenyl)-4-phenyl-pyrimido[1,2-a]indole-10-carboxylate (**3**) from 2-amino-1H-indole-3-carboxylates (**1**) and 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (**2**). Reaction conditions: (I) Cs_2CO_3/CH_3CN, reflux, 6 h, or Cs_2CO_3/CD_3CN in NMR probe at 348 K.

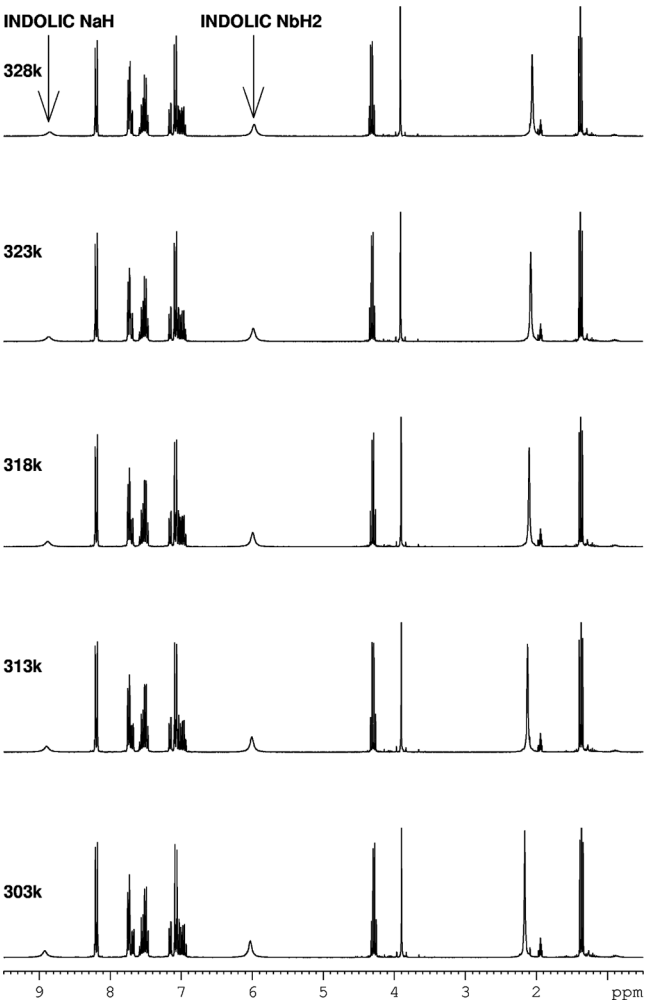


Figure 1. Stack plot of NMR resonances with different temperatures in the reaction mixture prior to the addition of the catalyst.

the product **3** within 45 min. Further we extended the reaction time up to 1 h 10 min as shown in Fig. 2.

The absence of the formation of other intermediates during the completion of reaction in NMR studies clearly indicated that the [3 + 3]-cyclocondensation reaction undergoes a concerted mechanism (Scheme 2).

The mechanism was further supported by monitoring the reaction with HR-MAS probe real-time NMR measurements using 50 µl of the total reaction mixture in deuterated acetonitrile (CD_3CN) under the same stoichiometric conditions in a 5-mm NMR tube, and the recording of the HR-MAS NMR spectra was carried out as soon as the spinning speed was achieved (4.0 kHz) with slight shimming in the *z* axis. Temperature range for monitoring the reaction

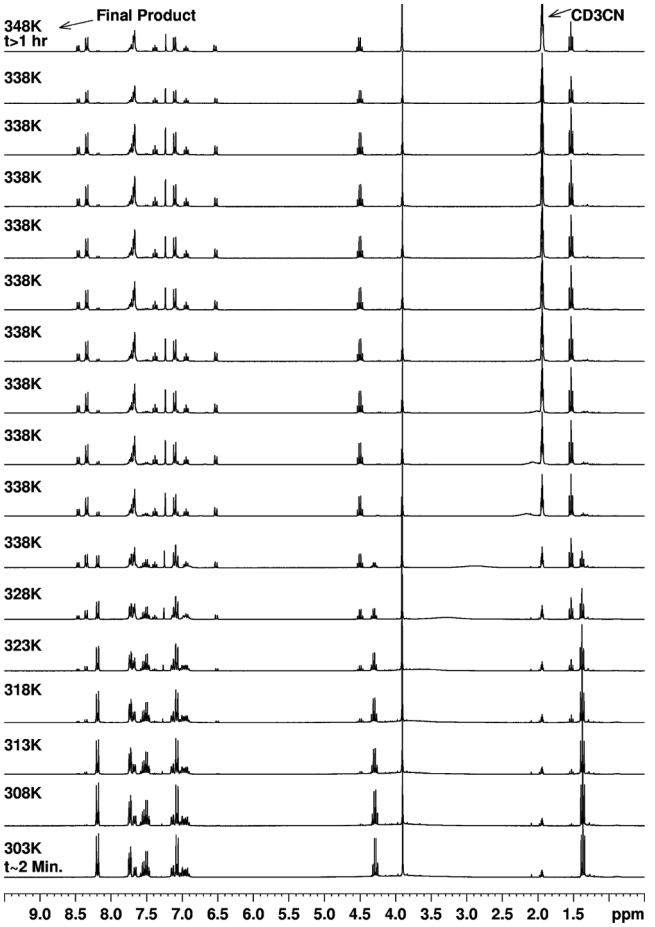
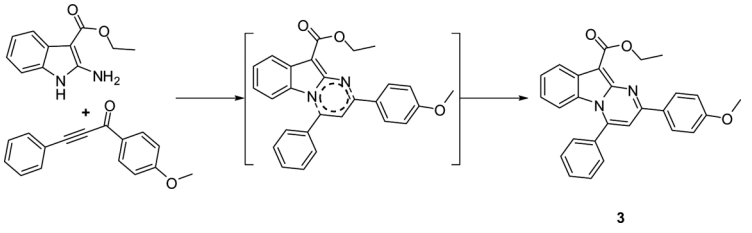


Figure 2. Stack plot of NMR resonances with different temperatures in the reaction mixture after addition of the catalyst.

was kept from 300 to 350 K. At 338 K, the time elasped is 45 min and this is the point for major product formation. After this point, product formation remains constant (Fig. 3).



Scheme 2. Concerted mechanism for the synthesis of 2-(4-methoxyphenyl)-4-phenyl-pyrimido[1,2-a]indole-10-carboxylate (**3**) via [3 + 3]-cyclocondensation reaction.

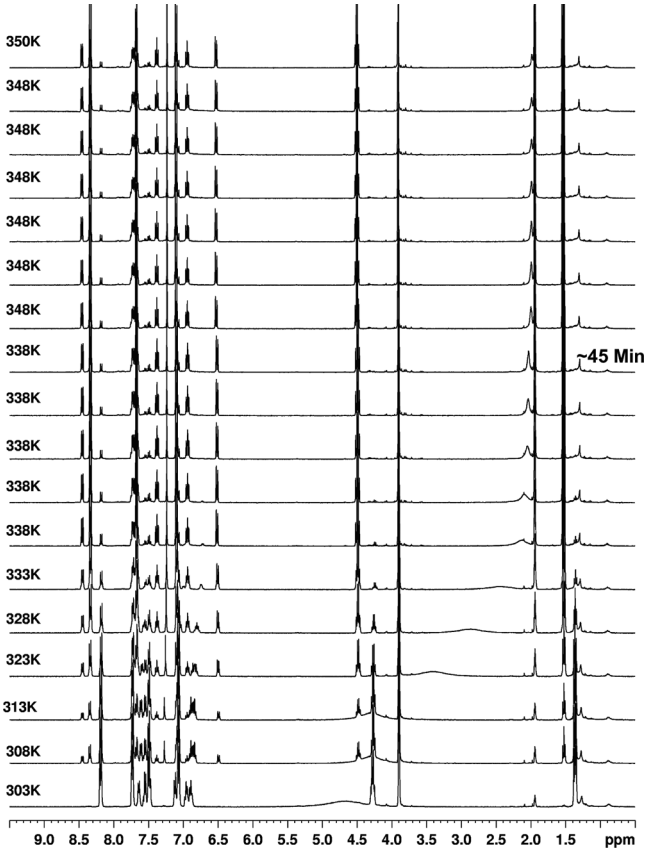


Figure 3. Stack plot of NMR resonances in HR-MAS probe with different temperatures in the reaction mixture after addition of the catalyst.

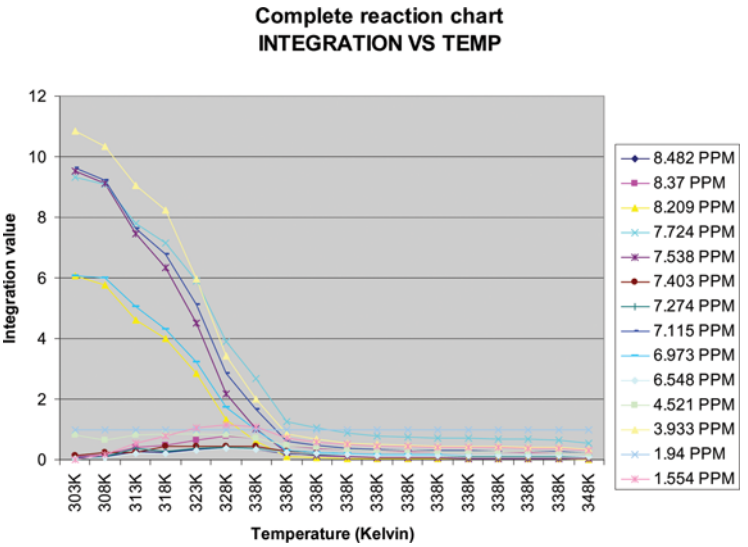


Figure 4. Complete reaction chart of integration vs. temperature. (Figure is provided in color online.)

The product formation started at 338 K as indicated by the variation in the integral area (Fig. 4). After increasing to 348 K, there was no variation in the integral area, which indicates that the reaction was completed at 338 K (optimum temperature) as shown in integration vs. temp chart (Fig. 4).

CONCLUSION

In summary, we have shown that the completion of the reaction using heterogeneous catalysis could be monitored using temperature-gradient real-time NMR spectroscopy. The reaction completion time and volume used are much shorter. Also, as no intermediate formation is observed in the ^{1}H NMR, we believe that reaction is achieved through concerted [3 + 3]-cyclocondensation mechanism.

EXPERIMENTAL

All the products were characterized by ^{1}H, ^{13}C, DEPT90, DEPT135, two-dimensional heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) spectroscopy. All the chemicals used in the study were purchased from Sigma Aldrich. The NMR spectra were recorded at room temperature as well as in different temperature ranges required for the completion of the reaction using Bruker Avance 400-MHz and Avance 300-MHz FT-NMR spectrometers equipped with a 5-mm multinuclear inverse, HRMAS probe, and QNP probe head with *z*-shielded gradient. Chemical shifts are given on the parts per million (ppm) scale and are referenced to tetramethylsilane (TMS) at 0.00 ppm for protons and for ^{13}C NMR spectra. Spectra recorded in CD_3CN solvent peak at 1.94, was taken as, a reference. In the one-dimensional measurements (^{1}H, ^{13}C, and DEPT) 32 K data points were used for the flame ionization detector (FID). The pulse programs of the following 2D experiments were taken from the Bruker software library and the parameters were as follows: 300/75 MHz gradient HSQC spectra: relaxation delay $d1 = 2$s; evolution delay $d2 = 3.44$ ms; 90° pulse, 6.85 μs for ^{1}H, 10 μs for ^{13}C hard pulses at −3.0 dB and 60 μs for ^{13}C globally optimized alternating phases of rectangular pulses (GARP) decoupling with gradient ratio GPZ1–GPZ2–GPZ3 = 50:30:40.1; 1024 data points in *t*2; spectral width 9.0 ppm in F2 and 160 ppm in F1; number of scans 32; 256 experiments in *t*1; linear prediction to 512; zero filling up to 1 K and apodization with sine bell in both dimensions prior to double Fourier transformation; 300/75 MHz gradient HMBC spectra: relaxation delay $d1 = 2$ s; delay of the low-pass J-filter $d2 = 3.44$ ms; delay for evolution of long-range coupling $d6 = 71$ ms with gradient ratio same as HSQC; 2048 data points in *t*2; spectral width 11.0 ppm in F2 and 240 ppm in F1; number of scans 52; 256 experiments in *t*1; linear prediction to 512; zero filling up to 2 K and apodization with 90° shifted square sine bell in F1 dimension and sine bell in F2 dimension prior to double Fourier transformation.

Procedure for the Synthesis of 2-(4-Methoxyphenyl)-4-phenyl-pyrimido[1,2-a]indole-10-carboxylate 3

Ethyl 2-amino-1*H*-indole-3-carboxylate (1.0 equiv, **1**), 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (1.0 equiv, **2**), and Cs_2CO_3 (1.5 equiv) were mixed in

acetonitrile and refluxed for 6 h. The progress of reaction was monitored by TLC and HPLC. After completion, the crude reaction mixture was extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure in vacuo. The crude reaction mixture was purified by column chromatography on 60 to 120-mesh silica using EtOAc/hexane (1:19) as eluent to afford **3**.

2-(4-Methoxyphenyl)-4-phenyl-pyrimido[1,2-a]indole-10-carboxylate (3)

Yield = 0.102 g (70%), orange solid, mp 138–140 °C, $R_f = 0.43$ (1:10 EtOAc–hexane); IR (KBr) ν_{max}, 3350, 2906, 2357, 1725, 1617, 1010 cm^{-1}; ^1H NMR (300 MHz, CD_3CN) $\delta = 8.46$ (1H, d, $J = 8.1$ Hz, ArH), 8.36 (2H, d, $J = 8.7$ Hz, ArH), 7.76–7.59 (5H, m, ArH), 7.40 (1H, t, $J = 7.8$ Hz, ArH), 7.30 (1H, s, ArH), 7.10 (2H, d, $J = 8.7$ Hz, ArH), 6.95 (1H, t, $J = 7.8$ Hz, ArH), 6.48 (1H, d, $J = 8.7$ Hz, Hz, ArH), 4.47 (2H, q, $J = 6.9$ Hz, OCH_2), 3.90 (3H, s, OCH_3), 1.53 (3H, t, $J = 6.9$ Hz, CH_3); ^{13}C NMR (75 MHz, CD_3CN) $\delta = 162.5$, 148.9, 133.9, 130.7, 130.5, 129.4, 129.2, 128.5, 128.2, 124.9, 121.2, 120.9, 114.9, 114.4, 105.2, 59.1, 55.3, 14.1 ppm; mass (ES^+) m/z 422.9 ($M^+ + 1$). Anal. calcd. for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63. Found: C, 76.75; H, 5.24; N, 6.65.

General Procedure for the ^1H NMR Analysis

To a solution of 2-amino-1*H*-indole-3-carboxylates (0.021 mmol) and 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (0.021 mmol) in 0.6 ml acetonitrile-d_3, Cs_2CO_3 (0.0318 mmol) was added in a 5-mm NMR tube spinning the sample at 20 Hz throughout the experiment, and after each temperature increment shimming of the compound was carried out.

General Procedure for the ^1H HR-MAS NMR Analysis

Cs_2CO_3 (0.0318 mmol) was added to a solution of 2-amino-1H-indole-3-carboxylates (0.021 mmol) and 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (0.021 mmol) in deuterated acetonitrile (40 µl) in a 50-µl 4-mm HR-MAS rotor, and the rotor was sealed by spacer and screw cap. The HR-MAS rotor was then directly inserted in the shimmed and tuned 4-mm $^1H/^{13}C$ HR-MAS dual probe. As soon as the spinning speed (4.0 kHz) was achieved, recording of the NMR data was carried out in a temperature range from 300 to 348 K.

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