

## THERMAL BEHAVIOR OF FUSED NH-PYRAZOLES UNDER FLASH VACUUM PYROLYSIS (FVP) CONDITIONS

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### Abstract

*In this article we report on the thermal reactions of 3-methyl-1(2),4,5,6-tetrahydrocyclopenta[c]pyrazole (1) and 1,10,10-trimethyl-5-trifluoromethyl-3,4-diazatricyclo[5.2.1.0<sup>2,6</sup>]deca-2(6),5(4)-diene (2) under FVP conditions. While in the first case all products arise from a nitrogen extrusion reaction, in the second one, ring isomerization is the principal reaction. The choice of these substrates has allowed continuing the research on the influence of substituents on the kinetics of the thermal reactions of pyrazoles.*

*Kinetic parameters for FVP reactions of 1 and of 3(5)-methyl,5(3)-phenyl-pyrazole (3) are also reported.*

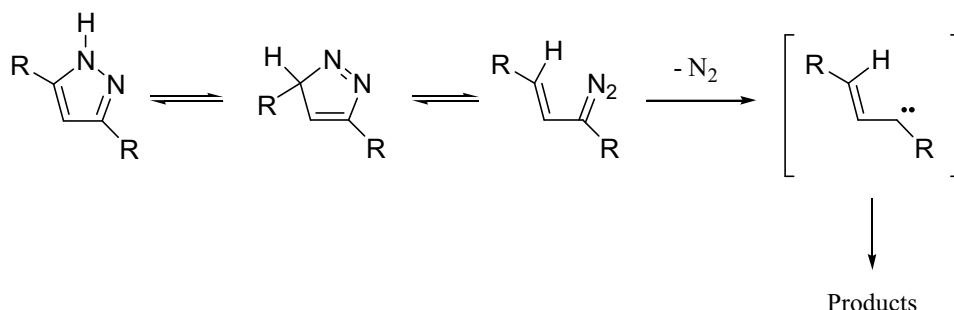
### Resumen

*En este trabajo se presentan las reacciones térmicas de flash vacuum pyrolysis (FVP) de 3-metil-1(2),4,5,6-tetrahidrociclopenta[c]pirazole (1) y 1,10,10-trimetil-5-trifluorometil-3,4-diazatriciclo [5.2.1.0<sup>2,6</sup>] deca- 2(6),5(4)- diene (2). En las reacciones de 1 se obtienen los productos correspondientes a la reacción de extrusión de nitrógeno mientras que, en el caso de 2 la reacción de isomerización de anillo es la reacción principal. El estudio de estos sustratos ha permitido investigar la influencia de la sustitución del pirazol en la cinética de la reacción térmica.*

### Introduction

Thermal reactions of NH-pyrazoles appear as a good alternative to the generation of vinylcarbenes by a nitrogen extrusion reaction, as these intermediates are difficult to obtain from other sources, such as thermal and photochemical reactions of cyclopropenes [1] and thermal reactions of vinyl diazomethanes [2]. The mechanism of thermal nitrogen extrusion reaction from pyrazoles includes several steps (Scheme 1) where nitrogen is lost from an intermediate vinyl diazomethane in the rate-limiting step [3]. In previous studies on this reaction it was established that vinyl carbene reactivity depends on ring substitution; thus products arising from H and R shifts, C-H insertion and addition to CO

bonds, may be obtained. In addition, kinetic measurements for nitrogen extrusion revealed that this reaction is also strongly influenced by ring substitution [4].



**Scheme 1**

As all of the previously described reactions were carried out with monocyclic pyrazoles, it was decided to study the effect of a fused ring on NH-pyrazole reactivity upon the Arrhenius parameters of this reaction. Thus, the results from flash vacuum pyrolysis (FVP) of 3-methyl-1(2),4,5,6-tetrahydrocyclopenta-[c]pyrazole (**1**) and reaction of 1,10,10-trimethyl-5-trifluoromethyl-3,4-diazatricyclo[5.2.1.0<sup>2,6</sup>]deca-2(6),5(4)-diene (**2**) are presented now. The Arrhenius parameters for decomposition of **1** and 3(5)-methyl, 5(3)-phenyl-pyrazole (**3**) are also reported to present a complete discussion of the influence of ring substitution on the activation parameters of the nitrogen extrusion reaction.

## Results and discussion

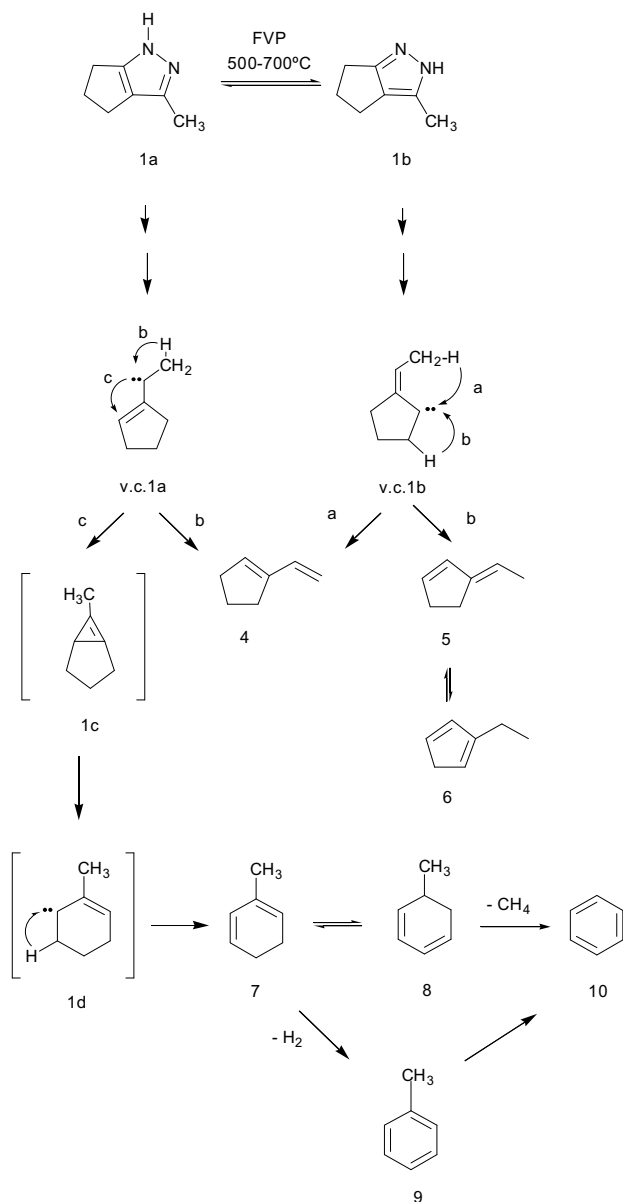
### FVP reactions of **1**

When pyrazole **1** was subjected to FVP in a conventional system (contact times around 10<sup>-2</sup> s and pressures of 10<sup>-2</sup> Torr) between 550-700°C, the only reaction found was extrusion of nitrogen and the principal products were a mixture of dienes **4-8**. Reaction products are shown in Scheme 2 and FVP conditions in Table 1.

T±1 [°C]	%Products				k [s <sup>-1</sup> ] <sup>a</sup>
	1	4+5+6	7+8	9+10	
570	76	24	0	0	33.9 ± 0.5
585	57	43	0	0	58.9 ± 0.4
615	30	46	21	3	83.6 ± 0.5
650	0	52	38	10	-

**Table 1.** FVP of **1**. <sup>a</sup>Averaged from four FVP experiments.

It should be noted that the products may be formed from the two different tautomers **1a** and **1b** present in the pyrazole **1**, as previously reported studies of other asymmetric pyrazoles.[4,5] Two vinylcarbenes (from now on vc) **1a** and **1b**, are proposed as the intermediates formed after the nitrogen extrusion reaction and responsible for the different products. These vinylcarbenes as well as their reaction pathways are presented in Scheme 2.



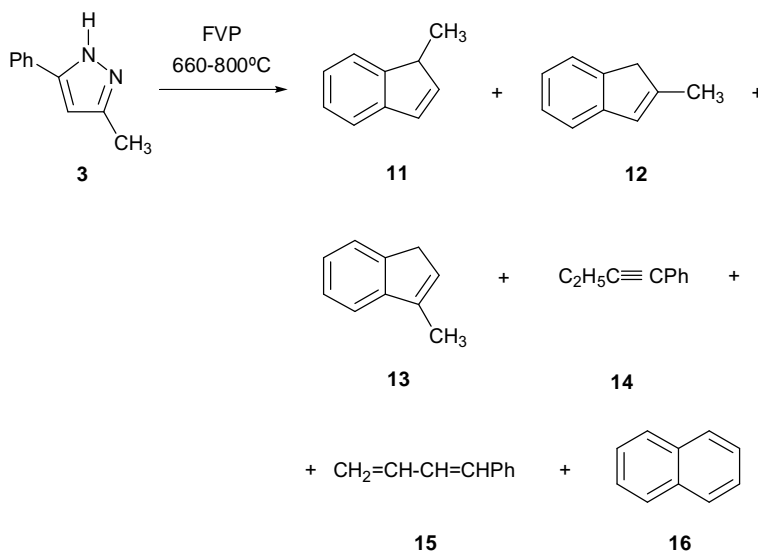
**Scheme 2**

Compound **4** could be formed via: (a) a 1,2-H shift in vc **1a**, (b) a 1,4-H migration in vc **1b** or from both pathways. As seen in Scheme 2, a 1,2-H shift in vc **1b** may give 3-ethylidenecyclopentene (**5**), which is known to isomerize to compound **6** under similar

reaction conditions [6]. The presence of 2-methylcyclohexadiene (**7**) can be explained through a 1,2-H shift in vc **1d**. This vinylcarbene may be formed from ring opening of the bicyclic cyclopropene intermediate (**1c**), which results from a cyclization of vc **1a**. These reactions are similar to those observed for a variety of cyclopropenes under pyrolytic conditions [7]. Diene **8** is probably obtained from the thermal isomerization of **7**. Furthermore, if vc **1b** affords a cyclization reaction as vc **1a**, the cyclopropene intermediate formed should give the starting vc **1b** by a ring opening reaction. Aromatic compounds such as toluene (**9**) and benzene (**10**) were also found in these experiments. While toluene could be formed by a radical dehydrogenation of **7**, benzene may be formed by CH<sub>4</sub> elimination from **8**, a loss of the methyl group from **9** or from both reactions. These elimination reactions (dehydrogenations-dealkylations) are quite common in high-temperature thermolysis, particularly if the final step leads to an aromatic compound [8]. The presence of radicals was confirmed by the formation of bibenzyl in reactions where toluene was used as carrier gas.

### Kinetic parameters for **1** and **3**

Table 1 shows the measured rate constants, averaged over four determinations, for thermal reactions of pyrazole **1**. Flash vacuum pyrolysis of **3** has been reported in a previous article [4] affording 1-methylindene (**11**), 2-methylindene (**12**), 3-methylindene (**13**), 1-phenylbut-1-yne (**14**), 1-phenylbutadiene (**15**) and naphthalene (**16**), the rate constants are reported now, averaged over four determinations. The results are given in Scheme 3 and Table 2. The amount of each product at the different temperatures was informed earlier.[4]

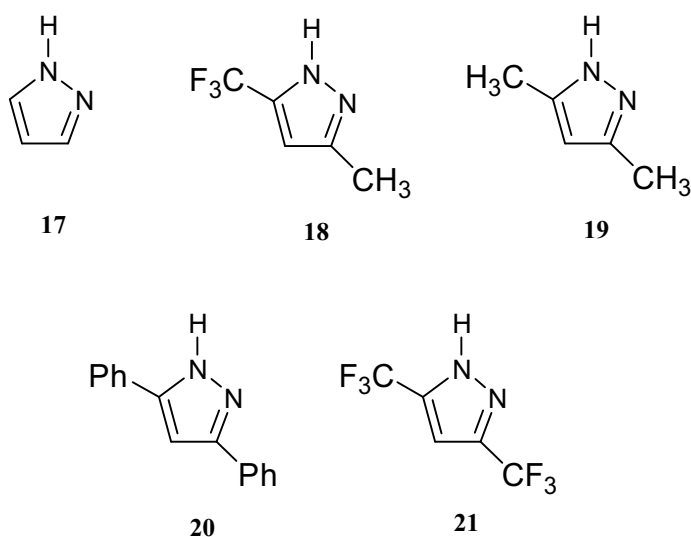


*Scheme 3*

$T \pm 1$ [ $^{\circ}\text{C}$ ]	% Conversion	$k$ [ $\text{s}^{-1}$ ] <sup>a</sup>
600	13	$17 \pm 1$
660	50	$112 \pm 4$
700	82	$360 \pm 13$

**Table 2.** FVP of **3**. <sup>a</sup> Averaged from four FVP experiments.

In Table 3, Arrhenius parameters of **1** and **3** are shown. Previously reported results for the pyrazoles in Figure 1 have also been included for comparison.[3-5] Looking at these results, it is evident that electron withdrawing and electron donating groups lower the energy of activation of the reaction in comparison with the parent pyrazole (**17**) (Figure 1). Pincock *et al.* [9] already noticed this effect in thermal reactions of phenyl-substituted vinyl diazomethanes.



**Figure 1**

Pyrazole	$E_a$ [kJ/mole]	Log A	Reference
<b>1</b>	$182 \pm 3$	$12.98 \pm 0.05$	This work
<b>3</b>	$217 \pm 2$	$14.18 \pm 0.08$	This work
<b>17</b>	$298 \pm 1$	$15.44 \pm 0.03$	3
<b>18</b>	$220 \pm 2$	$13.7 \pm 0.8$	5
<b>19</b>	$280 \pm 3$	$15.1 \pm 0.5$	3
<b>20</b>	$205 \pm 3$	$13.1 \pm 0.1$	4
<b>21</b>	$253 \pm 2$	$15.2 \pm 0.5$	5

**Table 3.** Kinetic parameters of different pyrazoles

According to the reaction mechanism for nitrogen extrusion reaction, asymmetric pyrazoles (**1**, **3** and 3(5)-methyl-5(3)-trifluoromethylpyrazole (**18**) (Figure 1) afford two different vinylcarbenes (see Scheme 2), which complicates the evaluation of the influence of the substituents on the energy of activation, although some considerations can be made.

The comparison of the  $E_a$  of **1** with the one of 3,5-dimethylpyrazole (**19**) (Figure 1), both of them dialkylpyrazoles, show that the corresponding to **1** is surprisingly lower than expected. This result may be ascribed to the strain effect of the fused ring, which may facilitate the ring opening reaction to the vinyl diazomethane isomer (Scheme 1). Electronic considerations cannot justify this difference.

The energy of activation of **3** is intermediate between the one of **19** and the one of 3,5-diphenylpyrazole (**20**) (Figure 1), which is a logic result. This is not the case when comparing the results of **18**, **19** and 3,5-bis-trifluoromethylpyrazole (**21**) (Figure 1), where an intermediate value for **18** was expected. As methyl and trifluoromethyl groups have opposite effects and as the reaction has several steps, it is not possible to evaluate each effect in each step.

### FVP reactions of **2**

FVP experiments carried out with **2** showed that it reacts between 500-700°C affording many products arising from isomerization, nitrogen extrusion, dimerization and radical decomposition reactions (Table 4 and Scheme 4). Even at low conversion conditions it was not possible to perform a complete separation and characterization of products from the reaction mixtures so they were only analyzed by GC/MS; that is the reason why only the mass degradation of each of the principal products are reported.

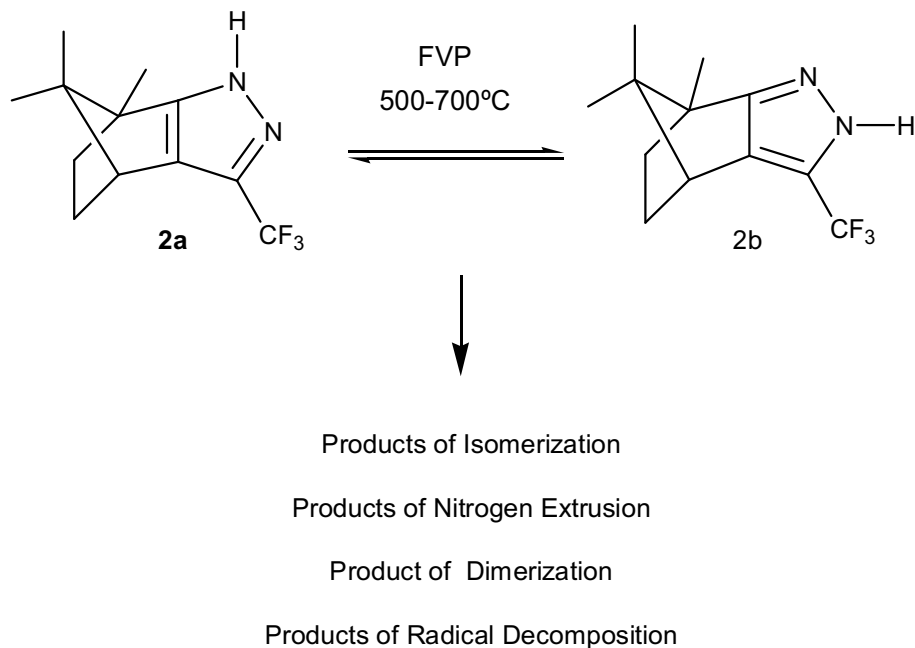
At 500°C four isomers of the starting material were detected (compounds **22-25**). At temperatures over 550°C two different compounds with molecular weights corresponding to loss of nitrogen from the starting pyrazole, compounds **26** and **27**, were found along with **22-25**.

T± 1 [°C]	% Conversion	Products <sup>a</sup>
500	22	<b>22</b> [ $m/z$ 244 ( $M^+$ , 5%)], <b>23</b> [ $m/z$ 244 ( $M^+$ , 5%)], <b>24</b> [ $m/z$ 244 ( $M^+$ , 3%)], <b>25</b> [ $m/z$ 244 ( $M^+$ , 22%)]
600	43	<b>22-25</b> , <b>26</b> [ $m/z$ 216 ( $M^+$ , 8%)], <b>27</b> [ $m/z$ 216 ( $M^+$ , 6%)]

**Table 4.** FVP of **2**. <sup>a</sup> Fragmentation and dimerization products are also detected.

Experimental evidence suggests that fragmentation and isomerization reactions of the aliphatic part on the pyrazole **2** possess lower energy of activation in comparison with nitrogen extrusion from the pyrazole ring.

In order to confirm these ideas, we carried out a test reaction using camphor. At 600°C, ten isomers of camphor were present in the pyrolyzate. This result points out the low thermal stability for this type of cyclic systems under FVP conditions [10].



*Scheme 4*

## Conclusions

The FVP study of **1** reveals that nitrogen extrusion is the principal reaction. The identified products arise from the different rearrangements of the vc involved. These intermediates are generated from the two possible tautomeric pyrazoles and can undergo 1,2 or 1,4 H-migration and C-H insertion reactions.

The values of the kinetic parameters for FVP of **1** reported here are lower than those found for other pyrazoles. Thus, the release of strain energy in the ring opening of the cyclopentane ring accelerates the reaction, raising the energy of the ground state.

The different thermal behavior of pyrazole **2** under FVP conditions indicates that isomerization reactions of the hydrocarbonated part are favored over the extrusion ones.

## Experimental Section

Reactions were carried out in a vycor glass flash vacuum thermolysis apparatus, using a GAYNOR PRDH temperature controller and a Thermolyne 21100 furnace. Oxygen free dry nitrogen or a nitrogen/toluene mixture was used as carrier gas. Samples to be pyrolyzed were of 30-50 mg. Products were trapped at liquid air temperature and after FVP experiments; products were extracted with the appropriate solvent and analyzed. Rates constants were evaluated for each individual reaction assuming first order. Four individual rate constants at each temperature were used to calculate the energies of activation. The amount of unreacted starting material was measured by <sup>1</sup>H-NMR using nitromethane as internal standard and it was between 20 and 80% depending on temperature. Contact times were calculated as  $V_0/\mu$ , being  $V_0$  the volume of the reactor in the hot zone and  $\mu$  the carrier gas flow at reaction conditions. Pressures were

measured before the cold trap. The confidence of kinetic results obtained in our system was proved by the measurement of kinetic parameters of FVP of 1-phenylethylacetate and compared with the ones reported for a static system [11]. In all reactions the mass balance was over 95%.

$^1\text{H}$  NMR spectra were recorded on a Bruker 200FT spectrometer and are expressed in  $\delta$  (ppm), downfield from TMS. Gas chromatography/mass spectrometry (GC/MS) analyses were performed on a Perkin Elmer Q-Mass 910 spectrometer equipped with a SE-30 column. The conversion values in the reactions of **1** and **3** were determined by quantifying substrate by  $^1\text{H}$  NMR using nitromethane as internal standard.

**FVP of 1.** Pyrazole **1** was prepared following one of the basic synthetic methodologies for pyrazoles synthesis from the literature [12] from 2-acetylcyclopentanone and hydrazine using methanol as the solvent. This compound was purified by re-crystallization in ethanol, m.p. 131-133°C.  $\delta_{\text{H}}$ (200 MHz;  $\text{CDCl}_3$ ) 2.26 (3H, s, Me), 2.52 (6H, m, 4,5 and 6-H), 7.80 (1H, br s, NH).  $\delta_{\text{C}}$ (200 MHz;  $\text{CDCl}_3$ ) 11.0, 21.8, 24.5, 28.0, 122.4, 133.8, 160.0;  $m/z$  122 ( $\text{M}^+$ , 94%), 107 (54), 94 (15), 80 (31), 52 (36), 42 (100).

Dienes **4–8** were identified by  $^1\text{H}$  NMR and GC/MS analysis and these results agree with previously reported values [13a-c]. Compounds **9** and **10** were identified by comparison with authentic samples.

**FVP of 2.** Pyrazole **2** was prepared from 3-(trifluoroacetyl)-*d*-camphor using the methodology described by Trofimenkov [14] for the synthesis of trifluoromethylpyrazoles. This pyrazole was purified by sublimation at low pressures. Mp 95-97°C;  $\delta_{\text{H}}$ (200 MHz;  $\text{CDCl}_3$ ) 0.87 (3H, s, 13-H), 0.90 (3H, s, 12-H), 1.34 (3H, s, 11-H), 2.12–2.45 (4H, m, 7 and 8-H), 3.18–3.39 (1H, m, 6-H), 10.35 (1H, broad s, NH).  $\delta_{\text{C}}$ (50 MHz;  $\text{DMSO-}d_6$ ) 21.3, 24.0, 25.9, 31.1, 42.2, 57.9, 64.2, 122.8 ( $\text{CF}_3$ , q, J220), 130.1, 151.0, 157.5;  $m/z$  244 ( $\text{M}^+$ , 6%), 229 (13), 201 (100), 181 (17), 167 (13), 53 (14), 42 (17), 41 (81), 39 (73). The entire crude of FVP reaction was extracted with  $\text{Cl}_3\text{CD}$  and analyzed by  $^1\text{H}$  NMR and CG/MS. Compound **22**:  $m/z$  244 ( $\text{M}^+$ , 5%), 229 (14), 209 (11), 201 (100), 181 (72), 167 (12), 41 (51). Compound **23**:  $m/z$  244 ( $\text{M}^+$ , 5%), 229 (11), 201 (86), 181 (66), 167 (11), 53 (18), 41 (100). Compound **24**:  $m/z$  244 ( $\text{M}^+$ , 3%), 201 (63), 181 (57), 77 (12), 53 (22), 43 (24), 41 (100), 39 (83). Compound **25**:  $m/z$  244 ( $\text{M}^+$ , 22%), 229 (17), 215 (10), 2201 (100), 181 (43), 43 (95). Compound **26**:  $m/z$  216 ( $\text{M}^+$ , 8%), 189 (41), 95 (11), 83 (16), 69 (10), 55 (39), 51 (15), 43 (27), 41 (100), 39 (65), 32 (14). Compound **27**:  $m/z$  216 ( $\text{M}^+$ , 6%), 189 (15), 55 (14), 43 (13), 41 (42) 39 (31), 32 (100).

**FVP of 3.** Pyrazole **3** was obtained as described in the literature.[15] The FVP reaction mixture was analyzed by column chromatography (petroleum ether and petroleum ether: chloroform, 60:40 as elution solvents) and the different isolated products afforded the following spectral data. Compound **11**:  $\delta_{\text{H}}$  (200 MHz;  $\text{DMSO-}d_6$ ) 1.33 (3H, d, J7, 1-Me), 3.15 (1H, q, J7, 1-H), 6.15 (1H, dd, J2 and 6, 2-H), 6.50 (1H, d, J6, 3-H), 7.10-7.42 (4H, m, Ph);  $m/z$  130 ( $\text{M}^+$ , 100%). Compound **12**:  $\delta_{\text{H}}$  (200 MHz;  $\text{DMSO-}d_6$ ) 2.18 (3H, s, 1-Me), 3.30 (2H, m, 1-H), 6.50 (1H, m, 3-H), 7.10-7.40 (4H, m, Ph) (10);  $m/z$  130 ( $\text{M}^+$ , 100%). Compound **13**:  $\delta_{\text{H}}$  (200 MHz;  $\text{DMSO-}d_6$ ) 2.25 (3H, s, 3-Me), 3.35 (2H, m, 1-H), 6.38 (1H, m, 2-H), 7.20-7.50 (4H, m, Ph); [16]  $m/z$  130 ( $\text{M}^+$ ,



100%). Compound **14**:  $\delta_{\text{H}}$  (200MHz; DMSO- $d_6$ ) 1.27 (3H, t, J8, 4-Me) 2.45 (2H, q, J8, 3-H), 7.10-7.80 (5H, m, Ph); [17]  $\nu_{\text{max}}$  2259  $\text{cm}^{-1}$  (C $\equiv$ C). Compound **15**:  $\delta_{\text{H}}$ (200 MHz; DMSO- $d_6$ ) 5.70 (2H, m, 4-H), 7.10 (3H, m, 1,2 and 3-H), 7.30-7.90 (5H, m, Ph). These results agree with previously reported values.[18] Compound **16** was identified by comparison with authentic samples.

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