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KF-Al_2O_3 as an Efficient and Recyclable Basic Catalyst for the Synthesis of 4*H*-Pyran-3-carboxylates and 5-Acetyl-4*H*-pyrans

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ABSTRACT

KF-Al_2O_3 as a recyclable basic catalyst for the three-component synthesis of 4*H*-pyran derivatives by the reaction of aldehydes, malononitrile and active methylene dicarbonyl compounds in ethanol at room temperature is described. The protocol is environmentally benign and offers rapid access to a wide array of 4*H*-pyran heterocycles in good to excellent yields.
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Keywords: 4*H*-Pyran derivatives; Ethanol; KF-Al_2O_3; Room Temperature; Three-Component

1. Introduction

Functionalized pyran derivatives have received significant attention due to their important biological and pharmacological properties [1]. Amongst the pyrans, the 4*H*-pyrans, in particular, and their analogous heterocyclic scaffolds have been known to exhibit anti-coagulant, anti-cancer, diuretic, spasmolytic and anti-anaphylactic activities [2-3]. The pyran ring also forms a core unit in a number of natural products [4-5]. In view of their biological and pharmacological properties, the synthesis of 4*H*-pyran derivatives is highly important.

In general, 4*H*-pyrans are prepared by the one-pot condensation of an aldehyde, malononitrile and ethyl acetoacetate in presence of a catalyst. Although several catalysts have been established in affecting this synthesis, only a few reports the use of basic catalysts, for example, tetrabutylammonium bromide, (*S*)-proline, hexadecyltrimethylammonium bromide, and rare earth perfluorooctanoates [6-8]. In addition, many of the available protocols for the synthesis of 4*H*-pyrans [9-15] involve the use of hazardous solvents, long reaction time besides lacking in general applicability, especially for the synthesis of ethyl/methyl 6-amino-4-aryl-5-cyano-2-methyl -4*H*-pyran-3-carboxylates which are less explored. In a more general approach, Babu and co-workers have recently shown the synthesis of polyfunctionalized 4*H*-pyrans using Mg/La mixed oxide [16]. However, the protocol suffers from the disadvantage of having to use elevated temperatures. Therefore, the development of a cost effective, mild and environment friendly procedure for the preparation of these important 4*H*-pyran heterocyclic compounds with wider functionality still offers an attractive scope of research.

In addressing the challenge of green synthesis, multicomponent reactions catalyzed by solid-support materials have emerged as an efficient strategy in the recent years. In particular, the use of potassium fluoride coated with alumina (KF-Al_2O_3) has become popular due to its inherent basic nature and characteristic properties such as enhanced reactivity, selectivity, a straight forward work-up procedure and milder reaction conditions [17-18]. Some of the reported reactions which use the KF-Al_2O_3 combination include the Knoevenagel condensation, the Henry reaction, the Darzens reaction, the Wittig reaction, the Biginelli reaction, alkylation and elimination reaction [17]. Thus, in continuation of our previous work on solid-support reagents/catalysts and our interest in developing new synthetic methodologies [19-20], we have further extended the investigation of KF-Al_2O_3 and its catalytic activity for the synthesis of ethyl 6-amino-4-aryl-5-cyano-2-methyl-4*H*-pyran-3-carboxylates and 5-acetyl-2-amino-4-aryl-6-methyl-4*H*-pyran-3-carbonitriles.

2. Results and Discussion

Herein, we report an alternative and environmentally benign three-component synthesis of ethyl 6-amino-4-aryl-5-cyano-2-methyl-4*H*-pyran-3-carboxylates and 5-acetyl-2-amino-4-aryl-6-methyl-4*H*-pyran-3-carbonitriles by the reaction of aldehydes, malononitrile and active methyl-

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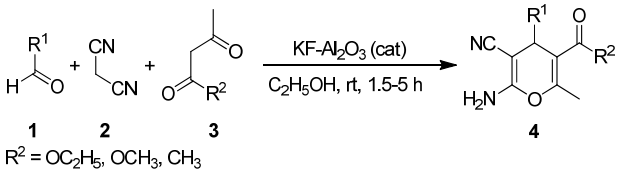
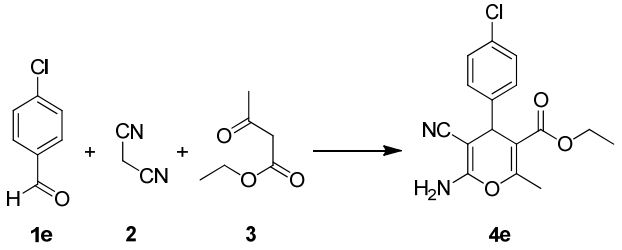
ene dicarbonyl compounds using KF-Al_2O_3 as a recyclable basic catalyst in ethanol at room temperature (**Scheme 1**).

In an initial experiment, the equivalent mixture of 4-chlorobenzaldehyde (1e) (1.00 mmol), malononitrile (2) (1.00 mmol), and ethyl acetoacetate (3a) (1.00 mmol) in presence of KF-alumina [52 mg (5 mol%), 40% potassium fluoride in Al_2O_3] in ethanol at room temperature proceeded to completion in 6 hrs and afforded a yield of 60% of the product 4e. In another attempt, when the same substrate mixture was reacted in presence of KF-Al_2O_3 (104 mg, 10 mol%), the yield of the product 4e increased substantially to 91% within 3 hrs. (entry 2, **Table 1**). However, on further increasing the amount of the catalyst to 15 mol% and 20 mol% respectively, no improvement in the yield was observed (entries 3 - 4, **Table 1**). This shows that the best yield of the product was obtained when the catalyst is taken at 10 mol%. In a controlled reaction the use of neutral alumina alone prolonged the formation of product 4e to 8 hrs. Alternatively, another reaction in methanol using 10 mol% of KF-Al_2O_3 at room temperature afforded 4e in 40% yield after stirring for 12 hrs (entries 5 - 6, **Table 1**).



Scheme 1: Three-component synthesis of 4*H*-pyran derivatives.

Table 1. Optimization of the KF-alumina with product 4e.



Entry	Reaction Conditions	Time (h)	Yield[a] (%)
1	KF-Al_2O_3 (5 mol%), EtOH, r.t	6	60
2	KF-Al_2O_3 (10 mol%), EtOH, r.t	3	91
3	KF-Al_2O_3 (15 mol%), EtOH, r.t	3	90
4	KF-Al_2O_3 (20 mol%), EtOH, r.t	2.5	85
5	Al_2O_3 (neutral, 5 mol%), EtOH, r.t	8	60
6	KF-Al_2O_3 (5 mol%), MeOH, r.t	12	40

[a]Isolated yield.

To examine the reusability of the catalyst, the KF-Al_2O_3, obtained after filtration from the previous reaction was thoroughly washed with ethyl acetate, dried and reused for the condensation of 4-chlorobenzaldehyde (1e), malononitrile (2) and ethyl acetoacetate (3a). It is interesting to note that the reaction afforded the product ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (4e) in 90% yield. The recyclability of the catalyst was further confirmed when it was found to exhibit good activity even after the fourth run with no major drops in the yield (**Table 2**).

Encouraged by this result, different substituted aldehydes were employed to prepare a series of ethyl 6-amino-4-aryl-5-cyano-2-methyl-4*H*-pyran-3-carboxylates (4) under the optimized reaction condition (**Table 3**). Irrespective of the presence of different substituents on the *ortho*- or *meta*- or *para*- positions of the ring of aromatic aldehyde, all the reactions proceeded to completion smoothly in 1.5 - 5 h to afford the corresponding products in good to excellent yields (4a-h, **Table 3**). The reactions involving halogen substituted aldehydes with malononitrile (2) and ethyl acetoacetate (3) afforded the desired products in 84% - 91% yields (entries 2 - 5, **Table 3**). Also, 4-hydroxybenzaldehyde (1f) and 4-methoxybenzaldehyde (1g) under the experimental condition furnished products 4f and 4g in 87% and 85% respecttively (entry 6 - 7, **Table 3**). On the other hand, aldehyde bearing nitro group such as 3-nitrobenzaldehyde (1h) could give the corresponding products 4h in 87% yield (entry 8, **Table 3**).

The wider scope of the methodology was studied by the preparation of methyl 6-amino-4-aryl-5-cyano-2-methyl-4*H*-pyran-3-carboxylates and 5-acetyl-2-amino-4-aryl-6-methyl-4*H*-pyran-3-carbonitriles by replacing methyl acetoacetate (3b) or acetylacetone (3c) as one of the components over ethyl acetoacetate (3a). Irrespective of the different substituents on the ring of aldehydes, all the reactions were effectively catalyzed by KF-Al_2O_3 (10 mol%) to afford the corresponding compounds 4i-j and 4l-q in good to excellent yields (entries 9 - 10 and 12 - 17,

Table 2. Recyclability results of KF-Al_2O_3 (10 mol%) with 4e.

Entry	Product	Reaction conditions	Time (h)	Yield[a] (%)
1	**4e**	KF-Al_2O_3 (recycled once), EtOH, r.t.	3	90
2	**4e**	KF-Al_2O_3 (recycled twice), EtOH, r.t.	3	87
3	**4e**	KF-Al_2O_3 (recycled third time), EtOH, r.t.	3.5	82[b]
4	**4e**	KF-Al_2O_3 (recycled fourth time), EtOH, r.t.	4.2	80[b]

[a]Isolated yield; [b]Purified by column chromatography.

Table 3. Three-component synthesis of 4*H*-pyran derivatives.

Entry	Substrate **1** (R^1)	Substrate **3** (R^2)	Time (h)	Product[c] **4**	Yield[a] (%)
1	C_6H_5 (**1a**)	OC_2H_5 (**3a**)	3	**4a** [16]	85
2	3-BrC_6H_4 (**1b**)	**3a**	3	**4b**	88
3	4-BrC_6H_4 (**1c**)	**3a**	3	**4c** [21]	90
4	2-ClC_6H_4 (**1d**)	**3a**	1.5	**4d** [22]	84
5	4-ClC_6H_4 (**1e**)	**3a**	3	**4e** [16]	91
6	4-HOC_6H_4 (**1f**)	**3a**	5	**4f** [16]	87[b]
7	4-$CH_3OC_6H_4$ (**1g**)	**3a**	3	**4g** [16]	85[b]
8	3-$NO_2C_6H_4$ (**1h**)	**3a**	3.5	**4h** [16]	87
9	**1e**	OCH_3 (**3b**)	3	**4i**	82
10	4-$CH_3C_6H_4$ (**1i**)	**3b**	1.5	**4j**	71
11	2-Furanyl (**1j**)	CH_3 (**3c**)	3.5	**4k**	72[b]
12	**1d**	**3c**	3	**4l**	82
13	4-CNC_6H_4 (**1k**)	**3c**	3	**4m**	85
14	**1i**	**3c**	3	**4n**	68
15	4-$NO_2C_6H_4$ (**1l**)	**3c**	3	**4o**	91
16	3,4-$(CH_3O)_2C_6H_3$ (**1m**)	**3c**	3	**4p**	67[b]
17	3,4,5-$(CH_3O)_3C_6H_2$ (**1n**)	**3c**	3	**4q**	63[b]

[a]Isolated yield; [b]Purified by column chromatography; [c]Literature references.

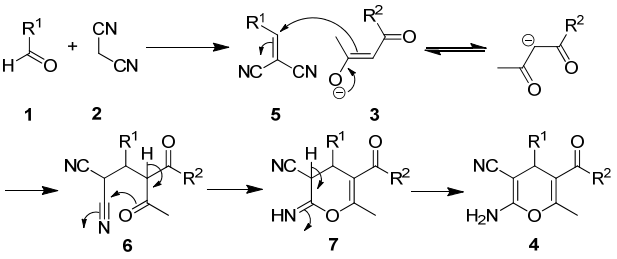
Table 3). Notably, the reaction with furan-2-carbaldehyde (1j) also proceeded smoothly to give the product 4k in good in 72% isolated yield, thus providing a broader application of the methodology.

All the products were purified by simple filtration of the reaction mixture and crystallization except in few cases where the purification was accomplished by column chromatography. The synthesized products (4a-q) were thoroughly characterized based on their ^{1}H NMR, ^{13}C NMR, IR, Mass spectroscopy and elemental analyses.

Mechanistically, the formation of the 4*H*-pyrans (4) takes place through the KF-Al_2O_3 catalyzed cyclization between the *in situ* formed Knoevenagel product 5 and the enolizable substrate 3. Evidently, this reaction pathway was further supported by the isolation of the Knoevenagel product 5 along with the product 4*H*-pyran 4e during the course of the condensation reaction (**Scheme 2**).

3. Conclusion

In summary, we have described an alternative and general method for the three component synthesis of functionalized 4*H*-pyran heterocycles using KF-Al_2O_3 (10 mol%) as a basic catalyst. The prospect of the reusabilityof KF-Al_2O_3 has also been demonstrated without compromising on the yield of the product. On the whole, the protocol presented here is an excellent alternative to many of the reported procedures by the use of KF-Al_2O_3 as an environmentally benign and recyclable catalyst.



Scheme 2. Plausible mechanism.

4. Experimental

All the melting points were taken by open capillary method and were uncorrected. The ^{1}H and ^{13}C NMR were recorded on Bruker *AVANCE*^{II} 400 MHz FT-NMR spectrometer with tetramethylsilane (TMS) as the internal standard using $CDCl_3$ and $(CD_3)_2CO$ as the solvents. The infra red (IR) spectra were obtained using Perkin-Elmer's FT-IR spectrophotometer. The mass spectra were recorded on Waters ZQ-4000 equipped with ESI and API mass detector. The Carbon, Hydrogen and Nitrogen (CHN) analysis was done on Perkin-Elmer PE 2400 Series II machine.

General experimental procedure: KF-Al_2O_3 (10 mol %) (104 mg) was added to a mixture of aldehydes (1) (2 mmol), malononitrile (2) (2 mmol) and active methylene dicarbonyl compounds (3) (2 mmol) in ethanol (6 mL). The reaction was stirred at room temperature for 1.5-5 h. On completion of the reaction, the catalyst was separated from the reaction mixture by filtration through a celite bed and thoroughly washing with ethanol. The combined organics was removed by evaporation under reduced pressure and the resulting 4*H*-pyran derivatives (4) were obtained in pure form after recrystallization or column chromatography.

Spectroscopic data: **Ethyl 6-amino-4-(3-bromo-phenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate** (4b) mp 165˚C - 167˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, J = 6.8 Hz, 3H, -$COOCH_2CH_3$), 2.31 (s, 3H, -CH_3), 3.92 - 4.05 (m, 2H, -$COOCH_2CH_3$), 4.34 (s, 1H, 4H), 4.51 (br, s, 2H, -NH_2), 7.05 - 7.13 (m, 2H, Ar-H), 7.24 - 7.29 (m, 2H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 18.5, 38.6, 60.8, 61.6, 107.4, 118.7, 122.6, 126.4, 130.1, 130.4, 130.6, 146.1, 157.3, 157.6, 165.5 ppm; IR (KBr) 1062, 1177, 1265, 1336, 1371, 1427, 1603, 1675, 1694, 2192, 2854, 2925, 2983, 3221, 3327, 3401 cm^{-1}; Mass (ES+) cald. for $C_{16}H_{15}BrN_2O_3$: 362.0; found m/z 362.9 (M + Na)$^+$ 384.9 (M + Na)$^+$; Anal. cald. for $C_{16}H_{15}BrN_2O_3$: C, 52.91; H, 4.16; N, 7.71 %; found: C, 52.79; H, 4.21 ;N,

7.86 %.

Methyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-methyl -4*H*-pyran-3-carboxylate (4i) mp 160˚C - 163˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (s, 3H, -CH_3), 3.53 (s, 3H, -$COOCH_3$), 4.35 (s, 1H, 4*H*), 4.47 (br, s, 2H, -NH_2), 7.07 (d, J = 8.4 Hz, 2H, Ar-H), 7.20 (d, J = 8.0 Hz, 2H, Ar-H), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5, 38.2, 51.8, 62.0, 107.5, 118.6, 128.8, 128.8, 133.0, 142.2, 157.3, 157.5, 166.2 ppm; IR (KBr) 1065, 1268, 1341, 1409, 1611, 1649, 1682, 1699, 2198, 2859, 2951, 3204, 3331, 3410 cm^{-1}; Mass (ES+) cald. for $C_{15}H_{13}N_2O_3$: 304.1; found m/z 304.8 $(M + H)^+$ 326.9 $(M + Na)^+$; Anal. cald. for $C_{16}H_{13}N_2O_2$: C, 59.12; H, 4.30; N, 9.19%; found C, 59.29; H, 4.41; N, 9.26%.

5-Acetyl-2-amino-4-(furan-2-yl)-6-methyl-4*H*-pyran-3-carbonitrile (4k) mp 173-175˚C; ^{1}HNMR ($(CD_3)_2CO$, 400 MHz) δ 2.10 (s, 3H, -CH_3), 2.19 (s, 3H, -$COCH_3$), 4.68 (s, 1H, 4H), 6.19 (d, J = 3.2 Hz, 1H, furanyl-*H*), 6.27 (br, s, 2H, -NH_2), 6.35-6.36 (m, 1H, furanyl-*H*), 7.46 (d, J =1.2 Hz, furanyl-*H*) ppm; ^{13}C NMR ($(CD_3)_2CO$, 100 MHz) δ 17.9, 28.7, 33.2, 58.3, 105.8, 110.4, 113.2, 118.5, 142.3, 155.8, 156.2, 159.5, 197.3; IR (KBr) 1012, 1064, 1173, 1206, 1250, 1322, 1414, 1603, 1654, 1674, 2189, 2854, 2926, 3220, 3331, 3400 cm^{-1}; Mass (ES+) cald. for $C_{13}H_{12}N_2O_3$: 244.1; found m/z 266.8 $(M + Na)^+$; Anal. cald. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47%; found: C, 63.99; H, 4.89; N, 11.38%.

5-Acetyl-2-amino-4-(2-chlorophenyl)-6-methyl-4*H*-pyran-3-carbonitrile (4l) mp 148-150˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97 (s, 3H, -CH_3), 2.22 (s, 3H, -$COCH_3$), 4.47 (br, s, 2H, -NH_2), 5.04 (s, 1H, 4*H*), 7.06-7.31 (m, 4H, Ar-*H*) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5, 29.1, 35.5, 59.8, 114.1, 118.5, 127.8, 128.6, 129.8, 129.9, 132.4, 140.4, 155.6, 158.0, 198.4 ppm; IR (KBr) 1222, 1377, 1588, 1659, 1689, 2195, 2925, 3199, 3322, 3384 cm^{-1}; Mass $(EI)^+$ cald. for $C_{15}H_{13}ClN_2O_2$: 288.1; found 310.9 $(M + Na)^+$; Anal. cald. % for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; N, 9.70 %; found C, 62.51; H, 4.50; N, 9.81 %.

5-Acetyl-2-amino-4-(4-cyanophenyl)-6-methyl-4*H*-py -ran-3-carbonitrile (4m) mp 182-184˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (s, 3H, -CH_3), 2.39 (s, 3H, -$COCH_3$), 4.52 (s, 1H, 4*H*), 7.26 (d, J = 8.0 Hz, 2H, Ar-*H*), 7.60 (d, J = 8.0 Hz, 2H, Ar-*H*), 8.23 (br, s, 2H, -NH_2) ppm; ^{13}C NMR ($CDCl_3$ + $(CD_3)_2CO$, 100 MHz) δ 198.1, 160.1, 160.0, 144.6, 132.1, 127.0, 117.2, 117.1, 113.5, 111.8, 68.4, 39.2, 29.4, 18.7; IR (KBr) 1059, 1253, 1379, 1602, 1700, 2194, 2225, 3207, 3331, 3416 cm^{-1}; Mass $(EI)^+$ cald. for $C_{16}H_{13}N_2O_2$: 279.1; found 301.9 $(M + Na)^+$; Anal. cald. for $C_{16}H_{13}N_2O_2$: C, 68.81; H, 4.69; N, 15.05%; found C, 68.89; H, 4.64; N, 16.00%.

5-Acetyl-2-amino-6-methyl-4-(4-nitrophenyl)-4*H*-pyran-3-carbonitrile (4o) mp 164-166˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15(s, 3H, -CH_3), 2.41 (s, 3H, -$COCH_3$), 4.58 (s, 1H, 4*H*), 7.32 (d, J = 8.4 Hz, 2H, Ar-*H*), 7.90 (br, s, 2H, -NH_2), 8.16 (d, J = 8.4 Hz, 2H, Ar-*H*) ppm; IR (KBr) 1222, 1346, 1664, 1681, 1702, 2192, 2924, 3198, 3340, 3442 cm^{-1} ; Mass $(EI)^+$ cald. for $C_{15}H_{13}N_3O_4$ 299.1; found 322.0 $(M + Na)^+$; Anal. cald. for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04 %; found C, 60.35; H, 4.29; N, 14.15 %.

5-Acetyl-2-amino-4-(3,4-dimethoxyphenyl)-6-methyl -4*H*-pyran-3-carbonitrile (4p) mp 168-170˚C; ^{1}HNMR ($CDCl_3$, 400 MHz) δ 2.05 (s, 3H, -CH_3), 2.34 (s, 3H, -$COCH_3$), 3.79 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 4.34 (s, 1H, 4*H*), 6.69-6.75 (m, 2H, Ar-H), 6.78 (s, 1H, Ar-H), 8.02 (br, s, 2H, -NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 29.6, 39.0, 55.9, 62.3, 110.5, 111.5, 114.8, 119.0, 119.5, 135.6, 148.4, 149.3, 154.8, 157.1, 199.0; IR (KBr) 1032, 1142, 1262, 1513, 1634, 1675, 2190, 2835, 3201, 3276, 3318, 3339, 3371 cm^{-1}; Mass $(EI)^+$ cald. for $C_{17}H_{18}N_2O_4$: 314.1; found 337.0 $(M + Na)^+$; Anal. cald. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91 %; found: C, 64.91; H, 5.85; N 8.99 %.

5-Acetyl-2-amino-6-methyl-4-(3,4,5-trimethoxyphenyl)-4*H*-pyran-3-carbonitrile (4q) mp 155-157˚C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.06 (s, 3H, -CH_3), 2.35 (s, 3H, -$COCH_3$), 3.76 (s, 6H, -OCH_3), 3.77 (s, 3H, -OCH_3), 4.33 (s, 1H, 4*H*), 6.30 (s, 2H, Ar-*H*), 7.34 (s, 2H, -NH_2) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 29.7, 39.6, 56.2, 60.8, 62.3, 104.3, 114.6, 118.9, 137.3, 138.5, 153.7, 154.9, 157.1, 198.8; IR (KBr) 1125, 1324, 1507, 1591, 1664, 1691, 2189, 2849, 2924, 3196, 3337, 3460 cm^{-1} ; Mass $(EI)^+$ cald. for $C_{18}H_{20}N_2O_5$: 344.1; found 367.0 $(M + Na)^+$; Anal. cald. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13 %; found: C, 62.73; H, 5.80; N, 8.20 %.

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