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A one-pot coupling–addition–cyclocondensation sequence (CACS) to 2-substituted 3-acylpyrroles initiated by a copper-free alkynylation†

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A novel three-component synthesis of 2-substituted 3-acylpyrroles can be initiated by a copper-free Pd-catalyzed alkynylation in a one-pot fashion. The reaction sequence proceeds under mild reaction conditions and in moderate to good yields with a broad scope of diversity.

Introduction

Pyrroles[1] are the basis of many pharmacologically active natural products.[2] In particular, 3-substituted derivatives are found in a wide variety of medicinal and agrochemical applications, such as efficient inhibitors of histone deacetylase,[3] HIV-1 transcriptase,[4] and COX-1/COX-2 cyclooxygenases.[5] Furthermore, per-substituted pyrroles are potent hypocholesterolemic agents inhibiting HMG-CoA reductase, a key enzyme in the biosynthesis of cholesterol.[6] Besides a wide range of applications in medicinal chemistry pyrroles are also found to be electronically polarizable and oxidizable building blocks for polymeric and supramolecular structures for applications in nonlinear optics.[7]

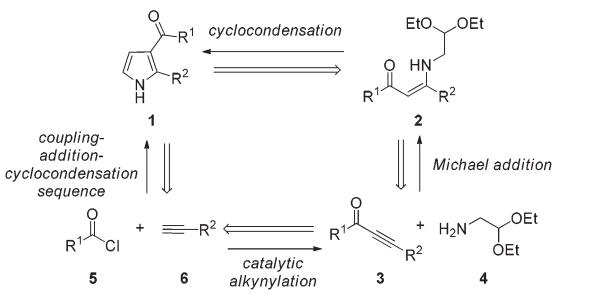
The most common methods rely on classical condensation reactions, such as the Hantzsch,[8] the Paal–Knorr,[9] and the Knorr pyrrole syntheses.[10] In addition, many uni- and bimolecular pyrrole syntheses have been established.[11–13] However, in recent years multicomponent approaches have been developed and promise very efficient, diversity oriented accesses to this important class of heterocycle.[14–16] Interestingly, only very few examples of 2-substituted 3-acylpyrroles are known. After the first example of a 3-trifluoracetyl pyrrole in 1992,[17] it was not until 2005 that Langer established a general route to 3-acylpyrroles.[18] Most interestingly, in this approach specifically substituted enaminones are directly transformed into 2-substituted 3-acylpyrroles.

Based upon our catalytic access to ynones[19] and their one-pot transformation into enaminones[20] and heterocycles[21] we reasoned that a three-component synthesis of 2-substituted 3-acylpyrroles should be readily accessible. Furthermore, our just recently developed copper-free catalytic alkynylation as an entry to ynones[22] sets the stage for this endeavor and here we report a novel consecutive one-pot three-component synthesis of 2-substituted 3-acylpyrroles.

Results and discussion

The retrosynthetic analysis of functionalized 3-acylpyrroles **1** (Scheme 1) suggests the corresponding *N*-(2,2-diethoxyethyl)-3-aminoalk-2-en-1-ones **2** as intermediates according to Langer's synthesis.[11] These enaminones can be directly disconnected to alkynones **3** and aminoacetaldehyde diethylacetal (**4**) *via* a retro-Michael step. The alkynones **3** stem from catalytic alkynylation of acid chlorides **5** with terminal alkynes **6** (Scheme 1).

Recently, we scouted, identified and optimized a copper-free Pd-catalyst system[23] for an efficient alkynone formation from acid chlorides **5** and terminal alkynes **6**,[22] which allows for a very flexible choice of solvents and still retains the advantages of the modified Sonogashira coupling.[19] The copper-free



Scheme 1 Retrosynthetic analysis and multicomponent synthetic concept for a coupling–addition–cyclocondensation synthesis of 2-substituted 3-acylpyrroles **1**.

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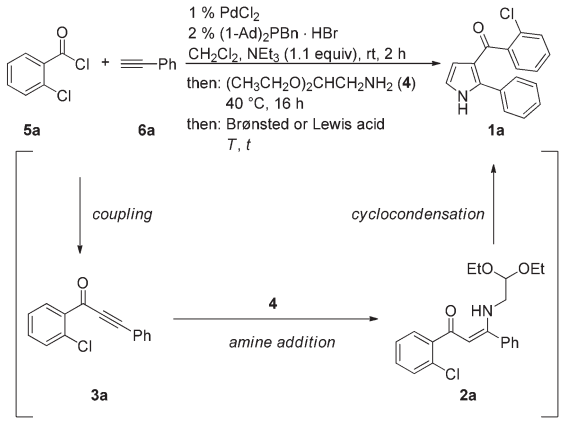
†Electronic supplementary information (ESI) available: Experimental details of the syntheses and analytical details of the compounds **1**. See DOI: 10.1039/c3ob41269e



Scheme 2 Model reaction for the optimization of the one-pot CACS synthesis of the 3-acylpyrrole **1a**.

catalyst system consists of 1 mol% of $PdCl_2$ and 2 mol% di-(1-adamantyl)-benzyl-phosphonium bromide (cataCXium® ABn·HBr)[24] in connection with reagent grade triethylamine as a base providing quantitative conversion within 24 h at room temperature depending on the substrate structures. Dichloromethane was chosen as a solvent for the complete reaction sequence, as in the final step the acetal should be activated by means of Brønsted or Lewis acid catalysis.

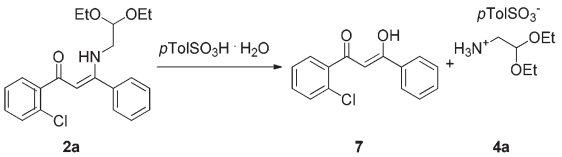
For the optimization of the novel coupling–addition–cyclocondensation sequence (CACS) a model system was chosen (Scheme 2). Upon reacting one equivalent of 2-chlorobenzoyl chloride (**5a**) and one equivalent of phenylacetylene (**6a**) under copper-free alkynylation conditions at room temperature[15] the intermediate alkynone **3a** was obtained within 2 h (monitored by TLC). Then, 1.03 equivalents of aminoacetaldehyde diethylacetal (**4**) were added to the reaction mixture and the alkynone **3a** was quantitatively converted into the corresponding β-enaminone **2a** within 16 h at 40 °C (monitored by TLC). For the optimization of the terminal cyclocondensation step various Brønsted and Lewis acids were tested in the sequence for furnishing the highest overall yields (Table 1).

First, Langer's conditions of the cyclocondensation were applied in the terminal reaction step at 0 °C and at room temperature (Table 1, entries 1 and 2). According to TLC a full conversion of the β-enaminone **2a** was achieved at 0 °C after 6 h and at room temperature after 4 h; however, the isolated yields of the target compound **1a** were only 9 and 11%, respectively. Reducing the amount of trifluoroacetic acid (TFA) to 5 equivalents showed no improvement in yield, although a quantitative conversion of **2a** was first observed after 23 h (Table 1, entry 3). Since TFA is a relatively strong acid (pK_a (water) ~ 0.23)[25] other carboxylic acids, such as acetic acid (pK_a (water) ~ 4.76),[25] formic acid (pK_a (water) ~ 3.77),[26] and dichloroacetic acid (pK_a (water) ~ 1.29),[25] were screened next (Table 1, entries 4–8). In neither case could a substantial increase of the yield of compound **1a** be achieved. The attempted cyclocondensation with acetic acid at 40 °C (oil bath) for 24 h eventually led to the complete recovery of β-enaminone **2a** (Table 1, entry 4). The

Table 1 Optimization study for the preparation of (2-chlorophenyl)(2-phenyl-1*H*-pyrrol-3-yl)methanone (**1a**)

Entry	Brønsted or Lewis acid (equivalents)	*T*	*t*	Yield of **1a**[a]
1	Trifluoroacetic acid (TFA) (10.0)	rt	4 h	11%
2	TFA (10.0)	0 °C	6 h	9%
3	TFA (5.0)	rt	23 h	5%
4	CH_3COOH (10.0)	40 °C	24 h	—
5	HCOOH (10.0)	40 °C	24 h	12%
6	Dichloroacetic acid (DCA) (10.0)	rt	4.5 h	5%
7	DCA (10.0)	40 °C	4 h	15%
8	DCA (10.0)	30 °C	4 h	9%
9	TMSOTf (1.0)	0 °C	24 h	—
10	TMSOTf (1.0)	rt	24 h	—
11	$FeCl_3$ (0.2)	rt	24 h	—
12	$pTolSO_3H{\cdot}H_2O$ (PTSA·H_2O) (2.5)	rt	18 h	53%
13	$MeSO_3H$ (2.6)	rt	23 h	33%
14	$MeSO_3H$ (2.0)	30 °C	17 h	51%
15	**$MeSO_3H$ (2.0)**	**40 °C**	**16 h**	**62%**
16	$MeSO_3H$ (2.0)	50 °C	23 h	59%
17	$MeSO_3H$ (1.5)	40 °C	24 h	59%
18	$MeSO_3H$ (3.0)	40 °C	4 h	50%

[a] All yields refer to isolated and purified products.

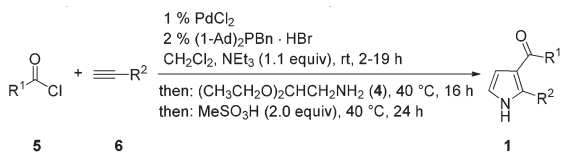


Scheme 3 Acid catalyzed hydrolysis of β-enaminone **2a** to give the β-hydroxy enone **7**.

application of the Lewis acids trimethylsilyltriflate (TMSOTf) and iron(III) chloride at 0 °C and at room temperature for 24 h also proved to be unsuccessful (Table 1, entries 9–11).

When *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) was employed in the final cyclisation step after 18 h at room temperature, an overall yield of 53% of **1a** was isolated (Table 1, entry 12). However, as a drawback the chemically bound water of PTSA caused a partial hydrolysis of the β-enaminone **2a** to give (*Z*)-1-(2-chlorophenyl)-3-hydroxy-3-phenylprop-2-en-1-one (**7**) as a byproduct (Scheme 3).[27]

Therefore, methanesulfonic acid ($MeSO_3H$), a similarly strong acid as PTSA·H_2O (pK_a ~ −1.9), was chosen.[28] Upon addition of 2 equivalents of $MeSO_3H$ in the final step at room temperature for 24 h a 33% overall yield of **1a** was isolated after column chromatography (Table 1, entry 13). At slightly elevated temperatures (30 or 40 °C oil bath) the isolated yields of **1a** could be raised to 51 and 62% (Table 1, entries 14 and 15). A further increase of the temperature did not give an additional increase of yields (Table 1, entry 16). Finally the employed equivalents of $MeSO_3H$ were varied. While a reduction to 1.5 equivalents had no particular changes in yields (Table 1, entry 17), the addition of 3 equivalents of $MeSO_3H$ let the reaction progress significantly faster; however, only a 50% overall yield of compound **1a** could be isolated (Table 1, entry 18).



Scheme 4 Variation of acid chloride **5** and alkyne **6** in the three-component CACS synthesis of 2-substituted 3-acylpyrroles **1**.

With this optimized protocol of a copper-free coupling–addition–cyclocondensation sequence (CACS) in hand we investigated the scope and limitations for this novel one-pot synthesis of 2-substituted 3-acylpyrroles **1** and the variations of the acid chlorides **5** and the alkynes **6** were studied (Scheme 4, Tables 2 and 3).

As previously reported the alkynone formation is strongly dependent on the electronic nature of the acid chlorides **5**; therefore, the quantitative coupling proceeds in a range of 2–19 h.[22] In addition to aroyl acid chlorides **5a–j** also heteroaroyl chlorides **5k–n** were successfully employed. With phenylacetylene (**6a**) as an alkyne component the corresponding 3-acylpyrroles **1a–n** were all isolated in moderate to excellent yields (11–73%) (Table 2). Interestingly, the overall yields are strongly dependent on the used aroyl chlorides **5**. The yields of **1** dropped significantly to 11–30% (Table 2, entries 3, 4, and 7) for electron-donating or slightly electron-withdrawing substituents in the *para*-position of the aroyl chloride. In contrast, strongly electron-withdrawing groups resulted in higher yields (Table 2, entries 8 and 9). The highest overall yields were obtained for *ortho*-halo-substituted aroyl chlorides. Therefore, it can be concluded that the electronic and stereoelectronic effect of the acid chloride **5** is crucial in the terminal step of the sequence, *i.e.* the acid catalyzed cyclocondensation. A strongly electron-withdrawing substituted enaminone is obviously stronger polarized in the ground state. The enaminones **2** decompose more rapidly upon addition of methanesulfonic acid when more electron-rich acid chlorides **15** are employed.

For the variation of the alkynes **6** the acid chloride component **1j** was kept constant (Table 3). The nature of the alkyne affects the rate of the initial coupling.[15] While the aromatic alkynes were fully consumed between 3 and 6 h (Table 3, entries 1–7), the aliphatic alkynes required a longer reaction time. Therefore, the coupling step was performed for 14–15.5 h, *i.e.* overnight (Table 3, entries 8 and 9). The corresponding 2-substituted 3-acylpyrroles **1o–w** were isolated in moderate to good yields (Table 3). The electronic effect of the substituents of the alkynes also affects the acid induced cyclocondensation reaction. While aliphatic substituents (Table 3, entries 8 and 9) furnish moderate yields of 30 and 46%, aromatic substituents give yields ranging from 21 to 69% (Table 3, entries 1–7). Electron-donating substituents in the *para*-position gave the same results as the electron neutral phenyl substituent (Table 3, entries 1 and 2 and Table 2, entry 10). Although the cyano substituent furnished a yield of 65% (Table 3, entry 3), the nitro substituent only gave rise to a

Table 2 Variation of acid chloride **5** in the three-component CACS synthesis of 2-substituted 3-acylpyrroles **1**[a]

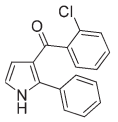
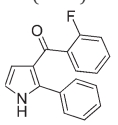
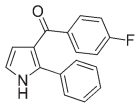
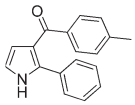
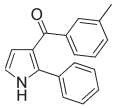
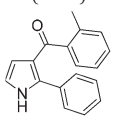
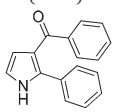
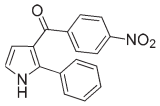
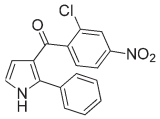
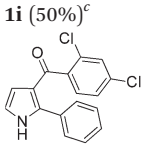
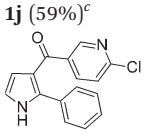
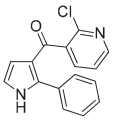
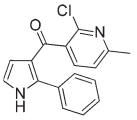
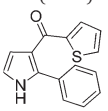
Entry	Acid chloride **5**	Alkyne **6**	3-Acylpyrrole **1** (yield)[b]
1	R^1 = *o*-ClC_6H_4 (**5a**)	R^2 = Ph (**6a**)	 **1a** (62%)[c]
2	R^1 = *o*-FC_6H_4 (**5b**)	**6a**	 **1b** (50%)[c]
3	R^1 = *p*-FC_6H_4 (**5c**)	**6a**	 **1c** (20%)[d]
4	R^1 = *p*-MeC_6H_4 (**5d**)	**6a**	 **1d** (11%)[d]
5	R^1 = *m*-MeC_6H_4 (**5e**)	**6a**	 **1e** (20%)[d]
6	R^1 = *o*-MeC_6H_4 (**5f**)	**6a**	 **1f** (26%)[d]
7	R^1 = Ph (**5g**)	**6a**	 **1g** (30%)[d]
8	R^1 = *p*-$O_2NC_6H_4$ (**5h**)	**6a**	 **1h** (43%)[d]
9	R^1 = 2-Cl-4-$O_2NC_6H_3$ (**5i**)	**6a**	 **1i** (50%)[c]
10	R^1 = 2,4-$Cl_2C_6H_3$ (**5j**)	**6a**	 **1j** (59%)[c]
11	R^1 = 2-Pyrid-5-yl (**5k**)	**6a**	 **1k** (43%)[d]

Table 2 *(Contd.)*

Entry	Acid chloride **5**	Alkyne **6**	3-Acylpyrrole **1** (yield)[b]
12	R^1 = 2-Pyrid-3-yl (**5l**)	**6a**	 **1l** (57%)[c]
13	R^1 = 2-Cl-6-Me-pyrid-3-yl (**5m**)	**6a**	 **1m** (73%)[c]
14	R^1 = 2-Thienyl (**5n**)	**6a**	 **1n** (36%)[c]

[a] All reactions were carried out on a 2 mmol scale (c_0(**5**) = c_0(**6**) = 1.0 M). [b] All yields refer to isolated and purified products. [c] The coupling step was performed at room temperature in 2–5 h. [d] The coupling reaction was performed at room temperature in 18–19 h.

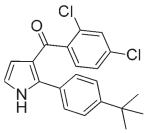
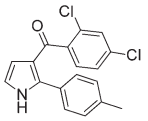
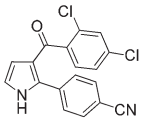
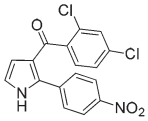
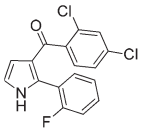
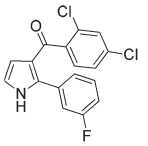
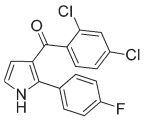
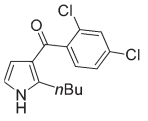
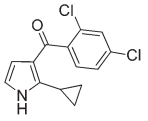
moderate yield of 21% (Table 3, entry 4). Obviously, side reactions of the intermediate β-enaminone **2** occurred in this case since an unidentified red product formed during column chromatography could not be eluted from the column.

Upon upscaling to 20 mmol, we noticed that the coupling reaction between acid chloride **5j** and terminal alkyne **6a** proceeds with a catalyst loading of 0.25 mol% of $PdCl_2$ and 0.5 mol% di-(1-adamantyl)-benzyl-phosphonium bromide (cataCXium® ABn·HBr) within the same reaction time. Furthermore, methanesulfonic acid was lowered from 2 to 1.5 equivalents. The overall yield of (2,4-dichlorophenyl)-(2-phenyl-1*H*-pyrrol-3-yl)methanone (**1j**) on a 20 mmol scale was found to be 57% (Scheme 5), almost identical to the yield of the 2 mmol scale, but the latter with a higher catalyst loading (Table 2, entry 10).

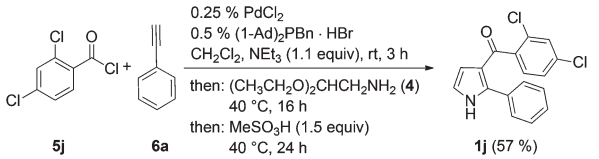
Conclusions

In conclusion we have developed a straightforward novel three-component synthesis of 2-substituted 3-acylpyrroles in a modular fashion. The sequence proceeds with easily available starting materials, which are consequently used in a strictly stoichiometric fashion, and under fairly mild reaction conditions of all three steps of the one-pot sequence. Furthermore, upon upscaling, the amount of the catalyst for the coupling step could be critically reduced into the 0.25 mol% regime; hence, the cost expensive palladium source will not have to be used in large quantities. Only the electron rich aroyl chlorides furnish overall moderate yields. Nonetheless, with these unparalleled mild reaction conditions and the overall efficient one-pot multistep synthesis in hand two points of

Table 3 Variation of alkyne **6** in the three-component CACS synthesis of 2-substituted 3-acylpyrroles **1**[a]

Entry	Acid chloride **5**	Alkyne **6**	3-Acylpyrrole **1** (yield)[b]
1	**5j**	R^2 = *p*-*t*BuC_6H_4 (**6b**)	 **1o** (59%)[c]
2	**5j**	R^2 = *p*-MeC_6H_4 (**6c**)	 **1p** (55%)[c]
3	**5j**	R^2 = *p*-NCC_6H_4 (**6d**)	 **1q** (65%)[d]
4	**5j**	R^2 = *p*-O_2NC_6H_4 (**6e**)	 **1r** (21%)[d]
5	**5j**	R^2 = *o*-FC_6H_4 (**6f**)	 **1s** (69%)[c]
6	**5j**	R^2 = *m*-FC_6H_4 (**6g**)	 **1t** (33%)[c]
7	**5j**	R^2 = *p*-FC_6H_4 (**6h**)	 **1u** (39%)[c]
8	**5j**	R^2 = *n*Bu (**6i**)	 **1v** (30%)[e]
9	**5j**	R^2 = Cyclopropyl (**6g**)	 **1w** (46%)[f]

[a] All reactions were carried out on a 2 mmol scale (c_0(**5**) = c_0(**6**) = 1.0 M). [b] All yields refer to isolated and purified products. [c] The coupling step was performed at room temperature in 3–4 h. [d] The coupling reaction was performed at room temperature in 5–6 h. [e] The coupling reaction was performed at room temperature in 15.5 h. [f] The coupling reaction was performed at room temperature in 14 h.



Scheme 5 CACS synthesis of (2,4-dichlorophenyl)(2-phenyl-1*H*-pyrrol-3-yl) methanone (**6j**) on a 20 mmol scale.

diversity could be readily explored. Now the stage is set for further methodological extensions towards differently *N*-substituted aminoacetaldehyde diethylacetals in the Michael step, which should furnish *N*-substituted 3-acylpyrrole analogues. These studies are currently underway.

Experimental

Typical procedure for the three-component synthesis of (2-chlorophenyl)(2-phenyl-1*H*-pyrrol-3-yl)methanone (1b)

Palladium(II) chloride (3.5 mg, 0.02 mmol, 1.0 mol%) and di-(1-adamantyl)benzylphosphonium hydrobromide (18.9 mg, 0.04 mmol, 2.0 mol%) were placed in a dry Schlenk tube under an argon atmosphere and dry dichloromethane (2 mL) was added. 2-Fluorobenzoyl chloride (**5b**) (360 mg, 2.00 mmol), phenylacetylene (**6a**) (209 mg, 2.00 mmol), and reagent grade triethylamine (0.30 mL, 2.15 mmol) were added to the mixture, and stirring at room temperature was continued for 2 h until complete conversion (monitored by TLC). Then, aminoacetaldehyde diethylacetal (**4**) (281 mg, 2.07 mmol) was added and the reaction mixture was stirred for 16 h at 40 °C (oil bath). Then, the reaction mixture was allowed to cool to room temperature and methanesulfonic acid (401 mg, 4.13 mmol) was successively added. After stirring for 24 h at 40 °C (oil bath) the reaction mixture was allowed to cool to room temperature. The solvents were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (*n* hexane–ethyl acetate 4 : 1) to give compound **1b** as a brownish red solid (265 mg, 50% yield). M.p. 118 °C; ^{1}H NMR (600 MHz, DMSO-d$_6$, rt): δ = 6.33 (t, J = 2.6 Hz, 1 H), 6.90 (t, J = 2.7 Hz, 1 H), 7.08–7.12 (m, 1 H), 7.15 (t, J = 7.4 Hz, 1 H), 7.25–7.31 (m, 3 H), 7.37–7.43 (m, 2 H), 7.44–7.47 (m, 2 H), 11.87 (s, 1 H). ^{13}C NMR (150 MHz, DMSO-d$_6$, rt): δ = 112.4 (CH), 115.6 (d, $^2J_{C-F}$ = 21.6 Hz, CH), 119.0 (CH), 120.6 (C_{quat}), 124.0 (d, $^3J_{C-F}$ = 3.1 Hz, CH), 127.7 (2 CH), 127.8 (CH), 128.9 (2 CH), 129.6 (d, $^2J_{C-F}$ = 15.5 Hz, C_{quat}), 129.8 (d, $^3J_{C-F}$ = 3.2 Hz, CH), 131.7 (C_{quat}), 131.9 (d, $^4J_{C-F}$ = 8.3 Hz, CH), 137.4 (C_{quat}), 158.8 (d, $^1J_{C-F}$ = 247.8 Hz, C_{quat}), 187.3 (C_{quat}). EI+MS (*m*/*z* (%)): 265.1 ([M$^+$], 67), 170.1 ([M$^+$ – C_6H_4F], 100), 142.1 ([M$^+$ – C_7H_4FO], 8), 123.0 ([M$^+$ – $C_{10}H_8N$], 9), 115.1 ([M$^+$ – C_8H_6FNO], 59), 95.0 ([M$^+$ – $C_{11}H_8NO$], 23). IR (diamond): $\tilde{\nu}$ [cm^{-1}] = 3233 (ν (N–H), m), 3109 (w), 2988 (m), 2972 (m), 2901 (m), 2795 (w), 1620 (s), 1609 (ν (C=O), s), 1578 (w), 1558 (w), 1474 (s), 1452 (s), 1431 (s), 1396 (s), 1362 (w), 1306 (m), 1290 (w), 1267 (w), 1225 (m), 1211 (w), 1177 (w), 1152 (w), 1101 (m), 1076 (m), 1057 (m), 999 (w), 901 (m), 885 (s), 812 (m), 787 (w), 756 (s), 739 (w), 721 (m), 689 (s), 677 (m), 654 (m), 613 (w). Anal. calcd for $C_{17}H_{12}FNO$ (265.3): C 76.97, H 4.56, N 5.28; Found: C 76.77, H 4.75, N 5.03.

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