Application of Polyphosphoric Acid-Mediated Acyl Migration for Regiospecific Synthesis of Diverse 2-Acylpyrroles from Chalcones

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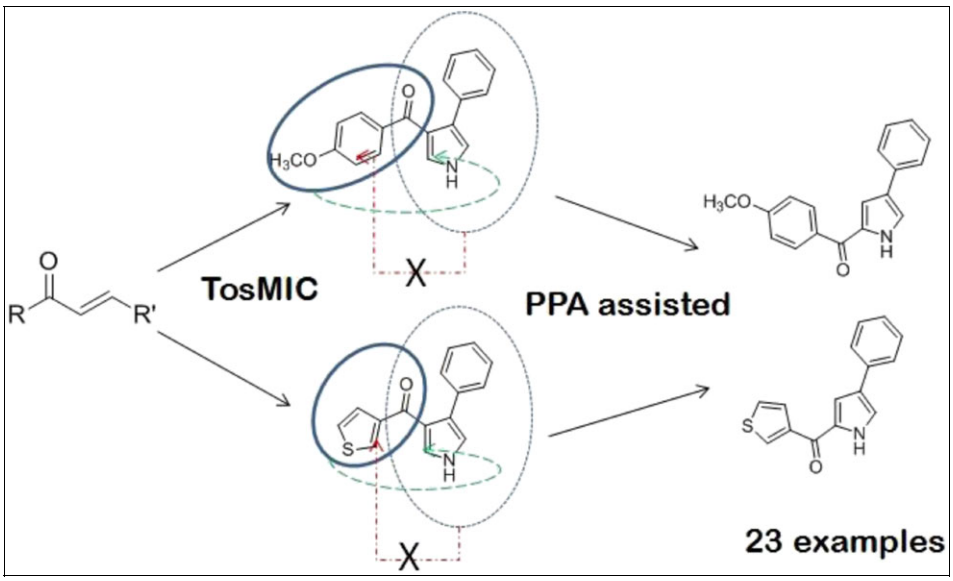


A metal-free approach for the synthesis of 2-acylpyrroles is reported in this paper. Synthesis of the target molecule started from chalcones and was carried out in two steps. Initial step involved the conversion of chalcones to corresponding 4-substituted-3-acylpyrroles by reaction with TosMIC. In the subsequent step, target molecules were obtained in modest to good yields by polyphosphoric acid-mediated acyl rearrangement of 3-acylpyrroles to their 2-acyl congeners. The crucial final step was amenable to diverse substitutions on pyrrole ring. Preliminary experiment for the determination of mechanism indicated the involvement of acylium ion.

INTRODUCTION

2-Acylpyrroles on their own or as part of a larger framework are known for a multitude of biological/biomedical properties ranging from non-steroidal anti-inflammatory drugs, antibiotics, to anticancer compounds [1–5]. Some important examples of this type of compounds include tolmetin, ketorolac, pyoluteorin, calcimycin, and diverse marinopyrroles (Fig. 1).

Acyl migrations within the molecular framework represent an important organic transformation used in multitude of synthetic strategies. Zamir *et al.* in a paper reported acid-catalyzed acyl rearrangement on a taxane, 9-dihydro-13-acetylbaccatin-III [6]. Ashfield and co-workers applied the chemoselective O-acyl to N-acyl migration in the Staudinger ligation for the synthesis of diverse amides [7]. In a paper by Arganat and co-workers, Friedel-Crafts acyl rearrangement, which is primarily a C-acyl to C-acyl migration, has been used for the synthesis of diverse acyl fluoranthene compounds [8]. The reported reactions were carried out in polyphosphoric acid (PPA) at various temperatures and resulted in the regioselective formation of the target molecules. Several other types of acyl rearrangement reactions are also known, which include base-induced Baker-Venkataraman and acid-catalyzed Fries rearrangements. Yu *et al.* reported the synthesis of multi-functionalized chromeno[2,3-*c*]pyrrol-9(2*H*)-ones from 1,3-diaryl-1,3-diketones and amino acids using 4-(dimethylamino)pyridine-catalyzed Baker–Venkataraman rearrangement as a key step [9]. Similar acyl migration was used by Fougerousse *et al.* for the synthesis of dibenzoylmethanes [10]. Fries rearrangement was used by Jeon and Magnion for the synthesis of hydroxyl aryl ketones using methanesulfonic acid and methanesulfonic anhydride [11]. Maeda *et al.* reported application of photo Fries rearrangement on pyrenyl esters [12]. Reported reaction was amenable to the presence of electron releasing/withdrawing groups as well

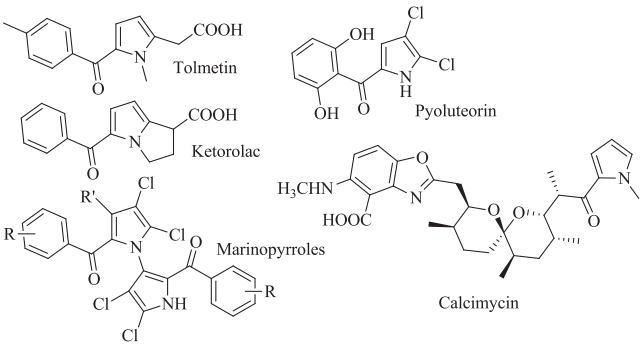


Figure 1. Examples of biologically active 2-acylpyrrole compounds.

as diverse heteroaromatic carboxylates. Base-promoted C → N acyl migration was used by Vicario and co-workers for the synthesis of nonproteinogenic tertiary and quaternary *N*-alkyl α-amino acids [13]. In a recent work by Kong *et al*., indolo[3,2-c]quinolinones were synthesized *via* a Pd/Cu catalyzed 1,2-acyl migration, starting from indole-2-carboxamides [14]. The methods reported thus clearly demonstrate the applicability of acyl rearrangement in diverse synthetic routes.

However, acyl rearrangement has been rarely used as a method for the preparation of 2-acylpyrroles. One of the very first examples of acyl rearrangement on pyrrole systems was reported by Palmer *et al*. in their attempt to cyclize various 3-(2-pyrrolyl)propanoic acids [15]. It was noticed that in the presence of PPA, the desired compound 4*H*-cyclopenta[*b*]pyrrole-4-ones and corresponding pyrrole-6-ones were obtained. Acyl rearrangement on pyrrole systems was also studied by Carson and Davis [16]. In their work, rearrangement of *N*-alkyl-2-acylpyrroles to corresponding *N*-alkyl-3-acylpyrroles was noticed in the presence of anhydrous trifluoroacetic acid. However, 2-acylpyrroles or 3-acylpyrroles bearing hydrogen on nitrogen resulted in an equilibrium mixture of both the acylated pyrroles, with their ratio dependent on the nature of the reaction medium. Dellemagne *et al*. in a separate paper has explored trifluoroacetic acid mediated synthesis 1-phenylpyrrole-3-carboxaldehydes from their 2-isomers using dichloroethane as a solvent [17]. The final products were obtained in good yields with very high regioselectivity. Acyl rearrangement of 2-acylpyrroles to their C-3 isomers was also noticed by Pina *et al*. in their attempt to carryout acylation of 1-nitrophenyl pyrroles, using acid anhydrides in the presence of catalytic amount of orthophosphoric acid [18]. Interestingly, most of the examples show rearrangement of 2-acyl systems to their 3-acyl congeners, and very few papers have highlighted the reverse process. Jefford and co-workers have reported the synthesis of 2-acylpyrroles by intramolecular delivery of acylium ion from their *N*-substituted mixed anhydrides to C-2 position of pyrroles [19]. These reactions were performed using the stoichiometric amount of $AlCl_3$ and dry Et_2O as a solvent in modest to good yields.

Based on the previous reports, we initiated studies on synthesis of diverse 4-substituted-2-acylpyrroles using rarely implemented acyl rearrangement. The simplicity of such a transformation and the possibility of introducing acyl group by avoiding unselective Friedel-Crafts/Vilsmeier-Haack reactions was an added attraction. A straightforward retrosynthetic strategy was conceived to start our investigation in this domain (Scheme 1). Compound **2** was envisaged as the substrate for the final step leading to **3**. Synthesis of compound **2** was supposed to be carried out by reaction between easily accessible chalcones (**1**) *via* van Leusen's pyrrole synthesis [20–23].

RESULTS AND DISCUSSION

Our initial synthetic efforts started from chalcones, which were converted to corresponding di-substituted pyrroles by reaction with well-known isonitrile source TosMIC in the presence of potassium tert-butoxide and DMSO as solvent at 25°C for 0.5 h. After fully characterizing the products, we embarked on a screening program to identify the most appropriate condition for their conversion to the target molecules (Table 1). For this purpose, phenyl(4-phenyl-1*H*-pyrrol-3-yl)methanone (**2a**) was chosen as the model substrate. As 1,2-acyl shift/migration was the desired goal of this work, choice of reaction conditions was based on Fries and other 1,2-acyl rearrangements reported in literature [8,11,24–27]. Thus, reactions were attempted with Lewis acids such as $AlCl_3$, $ZnCl_2$, and $FeCl_3$ (Entries 1–3). While no

Scheme 1. Retrosynthetic analysis of the target molecules.

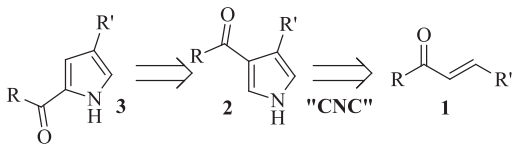
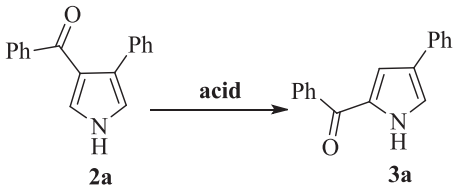


Table 1

Screening of reaction conditions for acyl migration.



2a **3a**

Entry	Acid (20 mol%)	Solvent	Temp. (°C)	Yield (%)[b]
1	$AlCl_3$	1,2-DCB	140	NR
2	$ZnCl_2$	1,2-DCB	140	NR
3	$FeCl_3$	1,2-DCB	140	66
4	$FeCl_3$	DCM	40	20
5	$FeCl_3$	THF	60	NR
6	$FeCl_3$	1,4-dioxane	110	NR
7	$FeCl_3$	$PhNO_2$	140	28
8	$FeCl_3$	Ph_2O	140	48
9	$FeCl_3$	1,2-DCE	85	NR
10	CH_3COOH	-	120	NR
11	CH_3COOH	1,2-DCB	140	NR
12	CH_3COOH	THF	140	NR
13	H_3PO_4	-	80	NR
14	H_3PO_4	1,2-DCB	140	34
15	CF_3SO_3H	THF	60	NR
16	HCl	THF	60	NR
17	PPA	1,2-DCB	140	NR
18[a]	PPA	-	110	73
19	PPA	PEG-400	110	NR

All the reactions were carried out for 12 h.
[a]Complete conversion was noticed in 30 min.
[b]Isolated yield. NR, no reaction.

conversion was noticed in case of $AlCl_3$ and $ZnCl_2$, $FeCl_3$ gave the target molecule in 66% yield. The purified product was thoroughly characterized by ^1H NMR and ^{13}C NMR, prior to further optimization of reaction conditions. ^1H NMR of compound **3a** revealed downfield shift of NH peak to 12.25 ppm from 11.64 ppm in **2a**, which indicated the presence of an electron-withdrawing group on the adjacent carbon. Additionally, disappearance of C—H peak at position 2 and presence of a proton at carbon-3 indicates rearrangement of acyl group to the second position of pyrrole. ^{13}C NMR further substantiated the proof for acyl rearrangement as carbonyl peak underwent a 6.5 ppm downfield shift to 184.2 ppm. Single crystal X-ray crystallography further ascertained the structure of compound **3a** (CCDC number 1859629) as shown in Figure 2. The pyrrole ring and phenyl ring substituted to the pyrrole ring are almost coplanar with dihedral angle C11-C10-C12-C13 = 0.36° only. The phenyl ring plane, which is attached to the carbonyl group, is deviating 40.83° from the pyrrole ring plane. The molecules form a hydrogen-bonded dimer with pyrrole N—H as donor and the carbonyl oxygen atom as acceptor with N—H … O non-covalent hydrogen

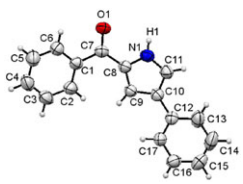


Figure 2. The ORTEP diagram of compound **3a**. The thermal ellipsoids are drawn with the 50% probability level. [Color figure can be viewed at wileyonlinelibrary.com]

bond length and D—H—A bond angle of 2.03 Å and 155.3° respectively.

Our initial success with $FeCl_3$ using 1,2-DCB as solvent prompted us to explore reactions with different solvents and reaction temperatures (Entries 4–9). While product formation was observed with DCM, $PhNO_2$, and Ph_2O, the yields obtained were lower compared with initial attempt with $FeCl_3$. Further screenings were carried out with Brönsted acids (Entries 10–19). Here, reaction was successful only with H_3PO_4 and PPA (neat), with PPA-mediated reaction giving the highest yield of 73%. Interestingly, when 1,2-DCB or PEG-400 were used as solvents in reactions involving PPA, no product

formation was noticed. Based on the previous results, we established the use of PPA (neat) at 110°C for 0.5 h as the best condition for the formation of 2-acylpyrrole (**3a**) from 3-acylpyrrole (**2a**).

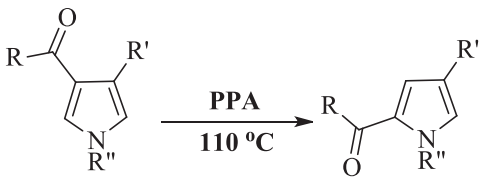
With the optimized conditions in hand, assortments of 4-substituted-3-acylpyrroles were used to explore the substrate scope of the reaction (Table 2). Reactions were initially attempted by varying the substituents at the fourth position of 3-benzoylpyrrole (**2a**–**g**). While all the aforementioned substrates were compatible, comparatively better yield was obtained with *p*-tolyl substituent. Substrate **2d** bearing *p*-nitrophenyl substituent provided the desired product in 53% yield. With mono/di-halogenated halogen phenyl substituents (**2e**–**g**), final products could be obtained in modest to good yields. Subsequent studies were conducted on 3-acylpyrroles bearing bi-phenyl, anthracen-9-yl, and methyl as substituents (**2h**–**j**). In these studies, an inverse relationship was shown between the size of the substituent and the yield of the reaction. *N*-Substituted systems (**2k**–**l**) on the other hand gave modest yield, indicating steric hindrance posed by the presence of substituent on pyrrole nitrogen.

Further studies were carried out to ascertain the effect of acyl groups on the feasibility/yield of the reaction (**2m**–**w**). Substrates with diverse benzoyl substituents indicated possible involvement of acyl carbocation in the reaction, as relatively high yields were seen with molecules bearing methyl and methoxy/di-methoxy groups as substituents (**3m**–**o**). In case of *p*-fluoro and *p*-chloro substituted benzoyl systems, comparatively low yields (25% and 52%, respectively) were recorded (**3p**–**q**). Applying the established conditions on naphthalen-2-yl(4-phenyl-1*H*-pyrrol-3-yl)methanone (**2r**) resulted in synthesis of the corresponding 2-acyl system (**3r**) in 55% yield. With 2-/3-thieno and 2-pyrido acyl systems (**2s**–**w**), rearranged products were obtained in 15–82% yields. Interestingly, with 3-acylthieno systems, only 2-acylpyrrole product was obtained and possible 2-acylthieno rearranged product was not seen. This result clearly demonstrates suitability of the method and its regiospecificity while generating rearranged 2-acylpyrrole product, even if corresponding C-2 positions are available in thiophene systems. Low yield in case of compound **3w** indicates destabilization of putative acyl carbocation, which is likely to form in the reaction. Similar observation is also noticed in case of compound **3p** containing *p*-fluoro substituent.

Based on the results obtained in the previous studies, an experiment was also conducted to understand the mechanism of acyl migration. Previous literature examples from pyrrole and indole systems have speculated formation of an acylium ion as well as internal transfer of acyl group [15,28]. Reaction was carried out on phenyl(4-phenyl-1*H*-pyrrol-3-yl)methanone in the presence of anisole, with 1:1 ratio of both the substrates. On completion, the reaction mixture was analyzed by ESI mass spectroscopy, which indicated formation of (2-methoxyphenyl)(phenyl)methanone/(4-methoxyphenyl)(phenyl)methanone [$M + H^+ = 213$] along with compound **3a** [$M + H^+ = 248$] (ESI). Based on this observation, a plausible mechanism has been proposed for the reaction

Table 2

Synthesis of diverse 2-acylpyrroles.

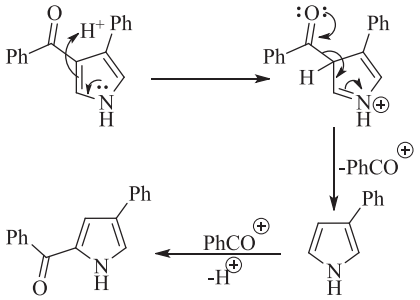


2 a-w **3 a-w**

3a R = Ph; R' = Ph; R" = H; **73%**
3b R = Ph; R' = (*p*-CH_3)Ph; R" = H; **74%**
3c R = Ph; R' = (*p*-OCH_3)Ph; R" = H; **37%**
3d R = Ph; R' = (*p*-NO_2)Ph; R" = H; **53%**
3e R = Ph; R' = (*p*-F)Ph; R" = H; **55%**
3f R = Ph; R' = (o, *p*-Cl, Cl)Ph; R" = H; **65%**
3g R = Ph; R' = (o, *p*-Cl, F)Ph; R" = H; **60%**
3h R = Ph; R' = (*p*-Ph)Ph; R" = H; **65%**
3i R = Ph; R' = anthracen-9-yl; R" = H; **22%**
3j R = CH_3; R' = Ph; R" = H; **73%**
3k R = Ph; R' = Ph; R" = CH_3; **35%**
3l R = Ph; R' = Ph; R" = CH_2Ph; **40%**
3m R = (*p*-CH_3)Ph; R' = Ph; R" = H; **64%**
3n R = (*p*-OCH_3)Ph; R' = Ph; R" = H; **53%**
3o R = (*m*, *p*-OCH_3, OCH_3)Ph; R' = Ph; R" = H; **63%**
3p R = (*p*-F)Ph; R' = Ph; R" = H; **25%**
3q R = (*p*-Cl)Ph; R' = Ph; R" = H; **52%**
3r R = naphthalen-2-yl; R' = Ph; R" = H; **55%**
3s R = thiophen-2-yl; R' = Ph; R" = H; **77%**
3t R = thiophen-2-yl; R' = (*p*-OCH_3)Ph; R" = H; **45%**
3u R = thiophen-2-yl; R' = (o, *p*-Cl, Cl)Ph; R" = H; **82%**
3v R = thiophen-3-yl; R' = Ph; R" = H; **79%**
3w R = pyridine-2-yl; R' = Ph; R" = H; **15%**

All the reactions were carried out for 30 min.

Scheme 2. Plausible mechanism for the conversion of 3-acylpyrrole to 2-acylpyrrole.



(Scheme 2). It is felt that protonation of carbon bearing the acyl group is the first step of this rearrangement, followed by cleavage of acyl group from pyrrole ring. Given the natural tendency of pyrrole ring to undergo electrophilic substitution reaction at the second position, the final step of this mechanism involves the reaction of acylium cation at the aforementioned position.

CONCLUSION

In conclusion, we have developed a simple strategy for the synthesis of diverse 2-acylpyrroles. Target molecules were synthesized in two steps, starting from easily accessible chalcones. Well-established van Leusen's pyrrole synthesis was used to perform the first step, whereas the final step involved application of seldom used acid-catalyzed acyl migration. The PPA-assisted method developed for the final step gave the desired products in modest to good yields and could be applied to diverse substituted pyrrole systems. The regiospecificity of the method towards C-2 position of pyrrole is demonstrated even when corresponding positions were available in activated phenyl and thiophene systems. A preliminary mechanistic study was also performed, which indicated involvement of acylium ion in generating the rearranged product.

EXPERIMENTAL

All the compounds and reagents required were purchased from commercial sources and were used without further purification. Solvents were dried and distilled using standard procedures, prior to use. ^{1}H NMR (300/400 MHz) and ^{13}C NMR (75.5/101 MHz) spectra were recorded in $CDCl_3$ and DMSO using $(CH_3)_4Si$ as internal standard. IR spectra were recorded as KBr plates on Jasco FT/IR-4200 instrument. Melting points were recorded on a Biotech India melting point apparatus and are uncorrected. Single-crystal X-ray studies were performed using CrysAlis PRO on a single crystal Rigaku Oxford XtaLab Pro diffractometer.

General procedure for the synthesis of compounds (3a–3w). To a 25 mL round bottom flask equipped with a stir bar was added appropriate 3,4-disubstituted pyrrole (0.5 mM) and PPA (2 mL). The reaction mixture was then allowed to stir for 30 min at 110°C under nitrogen atmosphere. It was subsequently cooled to room temperature and stirred with water (10 mL) for 30 min. The aqueous solution thus obtained was extracted with ethyl acetate (3 × 10 mL), and the ensuing organic layer was successively washed with brine and dried over anhydrous Na_2SO_4. Finally, the dried organic layer was concentrated under reduced pressure, and the residue obtained was purified by column chromatography.

Phenyl(4-phenyl-1H-pyrrol-2-yl)methanone (3a). Yield: 73%; white solid; mp 148–154°C; R_f 0.3 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3264, 1609, 1600, 1560, 1059; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16–7.21 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.54–7.59 (m, 2H), 7.62–7.68 (m, 3H), 7.73 (dd, *J* = 3.1, 1.6 Hz, 1H), 7.88–7.91 (m, 2H), 12.25 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 116.1, 124.0, 125.4, 126.2, 126.4, 128.9, 129.1, 131.7, 132.2, 134.8, 138.8, 184.2; ESI-MS (*m*/*z*): 248.0 [M + H]$^+$.

Phenyl(4-(p-tolyl)-1H-pyrrol-2-yl)methanone (3b). Yield: 74%; white solid; mp 152–158°C; R_f 0.4 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3262, 1623, 1571, 1146, 807; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H), 7.14 (dd, *J* = 4.8, 2.2 Hz, 3H), 7.56 (dd, *J* = 10.0, 7.9 Hz, 4H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.69 (dd, *J* = 3.1, 1.5 Hz, 1H), 7.87–7.91 (m, 2H), 12.22 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 21.1, 115.9, 123.7, 125.3, 126.2, 128.9, 129.1, 129.7, 131.6, 131.9, 132.1, 135.4, 138.9, 184.1; ESI-MS (*m*/*z*): 262.0 [M + H]$^+$.

4-(4-Methoxyphenyl)-1H-pyrrol-2-yl)(phenyl)methanone (3c). Yield: 37%; white solid; mp 118–124°C; R_f = 0.4 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3269, 3012, 1614, 1562, 1147; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.07 (s, 1H), 7.36 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.49–7.54 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.92–7.96 (m, 2H), 9.87 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.3, 114.2, 116.1, 121.5, 126.5, 127.0, 127.2, 128.4, 128.9, 131.6, 131.9, 138.3, 158.5, 184.8; ESI-MS (*m*/*z*): 278.0 [M + H]$^+$.

4-(4-Nitrophenyl)-1H-pyrrol-2-yl)(phenyl)methanone (3d). Yield: 53%; yellow solid; mp 206–212°C; R_f 0.5 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3264, 1504, 1627, 1111, 850; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.58 (dd, *J* = 7.2, 6.1 Hz, 2H), 7.64–7.70 (m, 1H), 7.91 (t, *J* = 1.7 Hz, 1H), 7.92 (s, 1H), 7.95–7.98 (m, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 8.00 (dd, *J* = 3.3, 1.6 Hz, 1H), 8.17 (dd, *J* = 6.8, 4.7 Hz, 2H), 12.53 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 116.7, 124.0, 124.5, 125.8, 126.0, 129.0,

129.2, 132.3, 132.4, 138.4, 142.0, 145.5, 184.4; HRMS-ESI (*m*/*z*): Calcd for $C_{17}H_{12}N_2O_3$ [M + H]$^+$ 293.0921 found 293.092.

(4-(4-Fluorophenyl)-1H-pyrrol-2-yl)(phenyl)methanone (3e). Yield: 55%; white solid; mp 108–114°C; R_f 0.3 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3259, 1625, 1587, 1562, 1205, 1076, 896; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.16 (dd, *J* = 11.1, 5.2 Hz, 3H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 6.8 Hz, 1H), 7.70 (dd, *J* = 8.6, 5.1 Hz, 3H), 7.89 (d, *J* = 7.9 Hz, 2H), 12.25 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 115.8, 116.1, 123.9, 125.2, 127.2, 128.9, 129.1, 131.4, 131.7, 132.2, 138.8, 161.2, 184.2; HRMS-ESI (*m*/*z*): Calcd for $C_{17}H_{12}FNO$ [M + H]$^+$ 266.0976 found 266.0974.

(4-(2,4-Dichlorophenyl)-1H-pyrrol-2-yl)(phenyl)methanone (3f). Yield: 65%; white solid; mp 92–98°C; R_f 0.4 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3264, 1736, 1626, 1561, 1294; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13–7.15 (m, 3H), 7.37 (dd, *J* = 8.4, 2.2 Hz, 3H), 7.54 (t, *J* = 7.4 Hz, 6H), 7.58–7.61 (m, 4H), 7.62 (d, *J* = 2.2 Hz, 3H), 7.66 (dd, *J* = 3.7, 2.1 Hz, 5H), 7.86–7.91 (m, 6H), 12.47 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 119.18, 121.87, 126.53, 127.94, 128.96, 129.14, 129.90, 131.03, 131.67, 131.87, 132.00, 132.34, 132.52, 138.65, 184.31; ESI-MS (*m*/*z*): 316.0 [M + H]$^+$.

(4-(2-Chloro-4-fluorophenyl)-1H-pyrrol-2-yl)(phenyl) methanone (3g). Yield: 60%; white solid; mp 106–120°C; R_f 0.3 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3410, 1614, 1559, 1123, 893; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.10 (dd, *J* = 2.4, 1.6 Hz, 1H), 7.23 (td, *J* = 8.5, 2.7 Hz, 1H), 7.47 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.59–7.65 (m, 2H), 7.65–7.70 (m, 1H), 7.85–7.91 (m, 2H), 12.41 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 115.1, 117.5, 119.3, 122.0, 126.3, 128.9, 129.1, 130.2, 130.9, 131.8, 132.2, 132.3, 138.6, 162.8, 184.2; HRMS-ESI (*m*/*z*): Calcd for $C_{17}H_{11}Cl_FNO$ [M + H]$^+$ 300.0586 found 300.0588.

(4-([1,1′-Biphenyl]-4-yl)-1H-pyrrol-2-yl)(phenyl)methanone (3h). Yield: 65%; light yellow solid; mp 198–204°C; R_f 0.5 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3266, 1611, 1565, 1287, 760; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.23–7.26 (m, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 6.7 Hz, 2H), 7.62–7.67 (m, 3H), 7.67–7.71 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.81 (dd, *J* = 3.1, 1.5 Hz, 1H), 7.95 (m, 2H), 12.31 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 116.1, 124.2, 125.7, 125.9, 126.8, 127.3, 127.6, 129.0, 129.2, 129.3, 131.8, 132.2, 134.0, 138.0, 138.8, 140.3, 184.2; HRMS-ESI (*m*/*z*): Calcd for $C_{23}H_7NO$ [M + H]$^+$ 324.1383 found 324.1389.

(4-(Anthracen-9-yl)-1H-pyrrol-2-yl)(phenyl)methanone (3i). Yield: 22%; light yellow solid; mp 122–128°C; R_f 0.4 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3278, 1608, 1572, 3038, 1122; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.98 (dd, *J* = 2.4, 1.5 Hz, 3H), 7.43–7.46 (m, 4H), 7.47 (d, *J* = 1.6 Hz, 3H), 7.48–7.54 (m, 14H), 7.59 (ddd, *J* = 7.4, 3.9, 1.3 Hz, 3H), 7.93 (d, *J* = 1.5 Hz, 3H), 7.95 (d, *J* = 4.5 Hz, 6H), 7.98 (s, 3H), 8.11 (d, *J* = 8.2 Hz, 6H), 8.60 (s, 3H), 12.59 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 121.1, 121.9, 125.7, 126.1, 126.6, 126.9, 127.8, 128.8, 128.9, 129.1, 130.5, 130.9, 131.4, 131.4, 132.2, 138.8, 184.2; HRMS-ESI (*m*/*z*): Calcd for $C_{25}H_{17}NO$ [M + H]$^+$ 348.1383 found 348.1383.

(4-Methyl-1H-pyrrol-2-yl)(phenyl)methanone (3j). Yield: 73%; brown solid; white solid; mp 144–150°C; R_f 0.3 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3198, 1630, 1568, 1217, 938; ^{1}H NMR (400 MHz, $CDCl_3$ + two drops of DMSO-d_6): δ 2.48 (s, 3H), 7.18 (d, *J* = 9.6 Hz, 1H), 7.20–7.26 (m, 1H), 7.36 (dd, *J* = 16.3, 8.6 Hz, 3H), 7.53 (t, *J* = 8.5 Hz, 2H), 10.71 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$ + two drops of DMSO-d_6): δ 25.6, 113.8, 121.9, 125.2, 126.2, 126.5, 128.8, 132.8, 134.5, 188.1; ESI-MS (*m*/*z*): 186.0 [M + H]$^+$.

(1-Methyl-4-phenyl-1H-pyrrol-2-yl)(phenyl)methanone (3k). Yield: 35%; yellow liquid; R_f 0.4 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3087, 1623, 1573, 1198, 723; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.00 (s, 3H), 7.03 (d, *J* = 1.9 Hz, 1H), 7.21–7.15 (m, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.55 (ddd, *J* = 8.1, 5.4, 1.1 Hz, 4H), 7.66–7.61 (m, 1H), 7.80 (dt, *J* = 3.8, 1.7 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 37.5, 118.8, 123.6, 125.2, 126.4, 128.8, 129.2, 129.3, 129.9, 130.9, 132.1, 134.3, 139.7, 185.5; HRMS-ESI (*m*/*z*): Calcd for $C_{18}H_{15}NO$ [M + H]$^+$ 262.1226 found 262.1229.

(1-Benzyl-4-phenyl-1H-pyrrol-2-yl)(phenyl)methanone (3l). Yield: 40%; light yellow liquid; R_f 0.5 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3410, 1614, 1559, 1123, 893; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.69 (s, 2H), 7.10 (d, *J* = 1.9 Hz, 1H), 7.21 (dd, *J* = 9.6, 2.7 Hz, 3H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.30–7.37 (m, 4H), 7.52 (dd, *J* = 10.3, 4.6 Hz, 2H), 7.58–7.64 (m, 3H), 7.74–7.79 (m, 2H), 8.00 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 52.0, 119.7, 124.2, 125.3, 126.6, 127.2, 127.7, 128.8, 128.9, 129.2, 129.4, 129.5, 130.4, 132.2, 134.1, 139.2, 139.6, 185.5; ESI-MS (*m*/*z*): 338.0 [M + H]$^+$.

(4-Tolyl)(4-phenyl-1H-pyrrol-2-yl)methanone (3m). Yield: 64%; white solid; mp 126–132°C; R_f 0.4 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3264, 3028, 1599, 1559, 894; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.15 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.43 (dd, *J* = 3.0, 1.5 Hz, 1H), 7.53 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 10.07 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 21.6, 116.1, 121.9, 125.3, 126.4, 127.3, 128.8, 129.1, 129.2, 131.8, 134.4, 135.5, 142.7, 184.7; ESI-MS (*m*/*z*): 262.0 [M + H]$^+$.

(4-Methoxyphenyl)(4-phenyl-1H-pyrrol-2-yl)methanone (3n). Yield: 53%; white solid; mp 184–190°C; R_f = 0.4 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3198, 1630, 1568, 1217, 938; ^{1}H NMR (400 MHz, $CDCl_3$): δ

3.90 (s, 3H), 6.99–7.01 (m, 1H), 7.02–7.03 (m, 1H), 7.14 (dd, J = 2.6, 1.6 Hz, 1H), 7.21–7.25 (m, 1H), 7.34–7.39 (m, 2H), 7.41 (dd, J = 3.0, 1.5 Hz, 1H), 7.53–7.55 (m, 2H), 7.97–7.98 (m, 1H), 7.99–8.01 (m, 1H), 9.88 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.5, 113.7, 115.5, 121.4, 125.3, 126.4, 127.2, 128.8, 130.8, 131.2, 131.8, 134.4, 162.9, 183.7; ESI-MS (*m*/*z*): 278.0 $[M + H]^+$.

(3,4-Dimethoxyphenyl)(4-phenyl-1H-pyrrol-2-yl)methanone (3o). Yield: 63%; white solid; mp 158–164°C; R_f 0.4 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3257, 1598, 1233, 1138, 812; ^{1}H NMR (400 MHz DMSO-d_6): δ 3.86 (d, J = 7.7 Hz, 6H), 7.12 (d, J = 8.4 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.22 (d, J = 3.8 Hz, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.42 (d, J = 1.9 Hz, 1H), 7.60 (dd, J = 8.3, 1.9 Hz, 1H), 7.64–7.70 (m, 3H), 12.16 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 55.9, 56.1, 111.4, 112.0, 115.4, 123.3, 123.4, 125.3, 125.9, 126.3, 129.1, 131.2, 131.8, 134.9, 148.9, 152.5, 183.0; HRMS-ESI (*m*/*z*): Calcd for $C_{19}H_7NO_3$ $[M + H]^+$ 308.1281 found 308.1282.

(4-Fluorophenyl)(4-phenyl-1H-pyrrol-2-yl)methanone (3p). Yield: 25%; white solid; mp 118–124°C; R_f 0.3 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3259, 1625, 1556, 1205, 896; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18–7.21 (m, 2H), 7.36 (dt, J = 15.5, 8.4 Hz, 4H), 7.65–7.69 (m, 2H), 7.75 (dd, J = 3.1, 1.5 Hz, 1H), 7.98 (dd, J = 8.8, 5.6 Hz, 2H), 12.27 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 115.8, 116.1, 124.1, 125.4, 126.3, 129.1, 131.5, 131.9, 134.7, 135.3, 164.6, 182.7; ESI-MS (*m*/*z*): 266.0 $[M + H]^+$.

(4-Chlorophenyl)(4-phenyl-1H-pyrrol-2-yl)methanone (3q). Yield: 52%; white solid; mp 150–156°C; R_f 0.4 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3270, 2359, 1610, 1589, 757; ^{1}H NMR (400 MHz DMSO-d_6): δ 7.19 (ddd, J = 8.4, 4.6, 1.3 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.60–7.65 (m, 2H), 7.67 (dd, J = 8.2, 1.1 Hz, 2H), 7.76 (dd, J = 3.1, 1.5 Hz, 1H), 7.88–7.95 (m, 2H), 12.30 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 116.4, 124.4, 125.4, 126.3, 126.4, 129.0, 129.1, 131.0, 131.4, 134.7, 137.0, 137.4, 182.8; ESI-MS (*m*/*z*): 282.0 $[M + H]^+$.

Naphthalen-2-yl(4-phenyl-1H-pyrrol-2-yl)methanone (3r). Yield: 55%; light yellow solid; mp 180–186°C; R_f 0.4 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3275, 1600, 1561, 1391, 899; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (t, J = 7.4 Hz, 1H), 7.30–7.32 (m, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.61–7.71 (m, 4H), 7.77 (dd, J = 3.1, 1.5 Hz, 1H), 7.94 (dd, J = 8.5, 1.7 Hz, 1H), 8.04 (d, J = 7.9 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.56 (s, 1H), 12.31 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 116.4, 124.0, 125.4, 125.6, 126.3, 126.4, 127.2, 128.1, 128.5, 128.6, 129.1, 129.9, 130.0, 131.9, 132.6, 134.8, 134.9, 136.1, 184.2; HRMS-ESI (*m*/*z*): Calcd for $C_{21}H_{15}NO$ $[M + H]^+$ 298.1226 found 298.1230.

(4-Phenyl-1H-pyrrol-2-yl)(thiophen-2-yl)methanone (3s). Yield: 77%; white solid; mp 120–126°C; R_f 0.3 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3289, 1583, 1271, 755, 500; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19–7.24 (m, 1H), 7.40 (dd, J = 10.6, 4.6 Hz, 4H), 7.57 (d, J = 7.2 Hz, 2H), 7.68 (d, J = 4.1 Hz, 1H), 7.99 (d, J = 2.8 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 114.5, 123.8, 125.4, 126.4, 129.1, 131.1, 132.9, 133.7, 134.8, 143.5, 175.2; ESI-MS (*m*/*z*): 254.0 $[M + H]^+$.

(4-(4-Methoxyphenyl)-1H-pyrrol-2-yl)(thiophen-2-yl) methanone (3t). Yield: 45%; white solid; mp 186–192; R_f 0.4 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3275, 1592, 1570, 809, 1247; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.77 (s, 3H), 6.91–6.95 (m, 2H), 7.29 (dd, J = 4.9, 3.8 Hz, 1H), 7.48–7.51 (m, 1H), 7.62 (dd, J = 3.1, 1.5 Hz, 1H), 7.64 (s, 1H), 7.66 (s, 1H), 8.00 (dd, J = 5.0, 1.0 Hz, 1H), 8.13 (dd, J = 3.8, 1.0 Hz, 1H), 12.14 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 55.5, 114.1, 114.5, 123.2, 126.3, 126.6, 127.4, 129.0, 130.9, 132.8, 133.6, 143.6, 158.2, 175.1; HRMS-ESI (*m*/*z*): Calcd for $C_{16}H_{13}NO_2S$ $[M + H]^+$ 284.074 found 284.0739.

4-(2,4-Dichlorophenyl)-1H-pyrrol-2-yl)(thiophen-2-yl) methanone (3u). Yield: 82%; white solid; mp 156–162°C; R_f 0.5 [hexane: ethylacetate = 4:1]; ν_{max} (KBr)/cm^{-1}: 3273, 1577, 1510, 291, 1136; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.28 (dd, J = 4.9, 3.8 Hz, 1H), 7.41 (dd, J = 8.4, 2.2 Hz, 1H), 7.51 (dd, J = 2.4, 1.6 Hz, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.64 (dd, J = 3.2, 1.5 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 8.00 (dd, J = 5.0, 1.0 Hz, 1H), 8.08 (dd, J = 3.8, 1.0 Hz, 1H), 12.44 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 117.5, 122.0, 126.3, 127.9, 129.0, 129.9, 130.5, 131.7, 131.9, 132.1, 132.5, 133.0, 133.9, 143.2, 175.3; HRMS-ESI (*m*/*z*): Calcd for $C_{15}H_9Cl_2NOS$ $[M + H]^+$ 321.9855 found 321.9855.

(4-Phenyl-1H-pyrrol-2-yl)(thiophen-3-yl)methanone (3v). Yield: 79%; white solid; mp 178–184°C; R_f 0.3 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3271, 1583, 1416, 1387, 819; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20 (t, J = 7.4 Hz, 1H), 7.30 (dd, J = 4.9, 3.8 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 7.58 (dd, J = 2.4, 1.6 Hz, 1H), 7.73 (dd, J = 9.4, 2.2 Hz, 3H), 8.15 (dd, J = 3.8, 1.0 Hz, 1H), 8.01 (dd, J = 5.0, 1.0 Hz, 1H), 12.24 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 114.5, 123.8, 125.4, 126.3, 126.4, 129.0, 129.1, 131.1, 132.9, 133.7, 134.8, 175.2; HRMS-ESI (*m*/*z*): Calcd for $C_{15}H_{11}NOS$ $[M + H]^+$ 254.0634 found 254.063.

(4-Phenyl-1H-pyrrol-2-yl)(pyridin-2-yl)methanone (3w). Yield: 15%; white solid; mp 158–164°C; R_f 0.5 [hexane: ethylacetate = 9:1]; ν_{max} (KBr)/cm^{-1}: 3267, 1636, 1502, 1133, 888; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.75 (s, 3H), 6.86 (d, J = 8.8 Hz, 2H), 7.02 (t, J = 2.2 Hz, 1H), 7.21 (dd, J = 5.0, 3.7 Hz, 1H), 7.26–7.34 (m, 2H), 7.50 (dd, J = 3.1, 2.0 Hz, 1H), 7.72 (dd, J = 3.7, 1.1 Hz, 1H), 7.93 (dd, J = 5.0, 1.1 Hz, 1H), 11.61 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ 122.2, 123.4, 126.7, 127.6,

128.1, 130.3, 130.7, 132.6, 133.0, 135.9, 137.8, 148.8, 155.9, 186.9, 189.0; HRMS-ESI (*m*/*z*): Calcd for $C_{16}H_{12}N_2O$ $[M + H]^+$ 249.1022 found 249.1024.

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REFERENCES AND NOTES

[1] Yuan, M.; Luo, M.; Song, Y.; Xu, Q.; Wang, X.; Cao, Y.; Bu, X.; Ren, Y.; Hu, X. Bioorg Med Chem 2011, 19, 1189.

[2] Cheng, C.; Liu, Y.; Song, H.; Pan, L.; Li, J.; Qin, Y.; Li, R. Mar Drugs 2013, 11, 2927.

[3] Grekov, I.; Pombinho, A. R.; Kobets, T.; Bartunek, P.; Lipoldova, M. Biomed Res Int 2017, 1.

[4] Kotagal, M.; Hakkarainen, T. W.; Simianu, V. V.; Beck, S. J.; Alfanso-Cristancho, R.; Flum, D. R. Ann Surg 2016, 263, 71.

[5] Cascioferro, S.; Raimondi, M. V.; Cusimano, M. G.; Raffa, D.; Maggio, B.; Daidone, G.; Schillaci, D. Molecules 2015, 20, 21658.

[6] Zamir, L. O.; Balachandran, S.; Zheng, Y. F.; Nedea, M. E.; Caron, G.; Nikolakakis, A.; Vishwakarma, R. A.; Sauriol, F.; Mamer, O. Tetrahedron 1997, 53, 15991.

[7] Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. Chem A Eur J 2012, 18, 14444.

[8] Malabi, T.; Shumel, C.; Pogodin, S.; Agranat, I. Struc Chem 2017, 28, 511.

[9] Yu, Y.; Hu, Y.; Shao, W.; Huang, J.; Zuo, Y.; Huo, Y.; An, L.; Du, J.; Bu, X. Eur J Org Chem 2011, 4551.

[10] Fougerousse, A.; Gonzalez, E.; Brouillard, R. J Org Chem 2000, 65, 583.

[11] Jeon, I.; Mangion, I. K Synlett 2012, 23, 1927.

[12] Maeda, H.; Akai, T.; Segi, M. Tetrahedron Lett 2017, 58, 4377.

[13] Ugarriza, I.; Uria, U.; Carrillo, L.; Vicario, J. L.; Reyes, E. Chem A Eur J 2014, 20, 11650.

[14] Kong, J.; Zheng, Z.; Tang, R.; Wang, M.; Sun, Y.; Li, Y. Org Lett 2018, 20, 5696.

[15] Palmer, M. H.; Leitch, D. L.; Greenhalgh, C. W. Tetrahedron 1978, 34, 1015.

[16] Carson, J. R.; Davis, N. M. J Org Chem 1981, 46, 839.

[17] Dallemagne, P.; Rault, S.; Fabis, F.; Dumoulin, H.; Robba, M. Synth Commun 1994, 24, 1855.

[18] Pina, M. C.; Budilin, V. A.; Rodrigues, M.; Bundel, Y. U. Chem Heterocycl Compd 1989, 25, 268.

[19] Jefford, C. W.; Tang, Q.; Boukouvalas, J. Tetrahedron Lett 1990, 31, 995.

[20] Van Leusen D.; Van Leusen, A. M. Org React, 2001, 57, 417 and the references therein.

[21] Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. Angew Chem Int Ed 2013, 52, 6953.

[22] Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. J Org Chem 2007, 72, 1246.

[23] Smith, N. D.; Huang, D.; Cosford, N. D. P. Org Lett 2002, 4, 3537.

[24] Bach, R. D.; Domagala, J. M. J Org Chem 1984, 49, 4181.

[25] Anderson, K. W.; Tepe, J. J. Tetrahedron 2002, 58, 8475.

[26] Martin, R. Org Prep Proced Int 1992, 4, 369.

[27] Tisserand, S.; Baati, R.; Nicolas, M.; Mioskowski, C. J Org Chem 2004, 69, 8982.

[28] Budylin, V. A.; Matveeva, E. D.; Kost, A. N. Chem Heterocycl Compd 1980, 9, 1280.

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