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NOVEL ONE-POT SYNTHESIS OF DIHYDROACENAPHTHO[1,2-*f*][1,3]-OXAZEPINES *VIA* 1,4-DIPOLAR CYCLOADDITION REACTION

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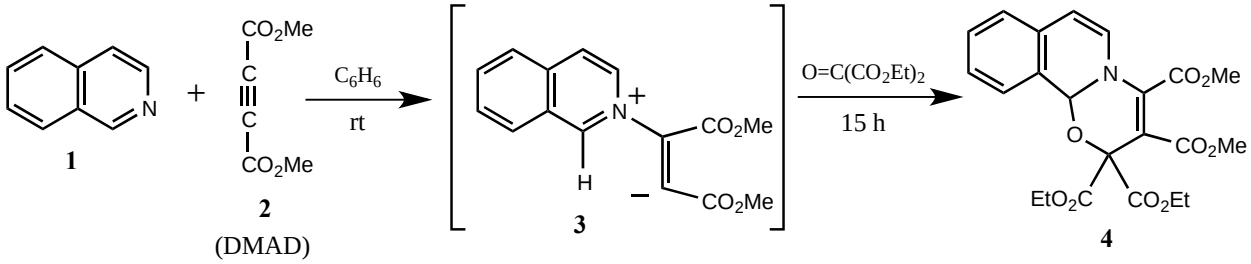
Dedicated with best wishes to Professor Dr. Wolfgang Voelter on the occasion of his 80th birthday

Abstract – A facile three-component reaction involving 3-alkyl(aryl)imidazo[1,5-*a*]pyridines **7a-g**, dimethyl acetylenedicarboxylate **2** (DMAD) and acenaphthene-1,2-dione **5** led to the construction of the respective dihydroacenaphtho[1,2-*f*][1,3]oxazepine-10,11-dicarboxylates **10a-g** in fair yields. Structures of the latter tetracyclic adducts, are based on NMR and MS spectral data and confirmed by single-crystal X-ray diffraction analysis for compound **10a**. Most logically, the reaction proceeds *via* initial formation of the relevant diastereomeric spiro[1,3]oxazine-1,4-dipolar cycloadducts **12**, **13** which then suffer skeletal rearrangement leading to the respective acenaphtho[1,2-*f*][1,3]oxazepines **10a-g**.

INTRODUCTION

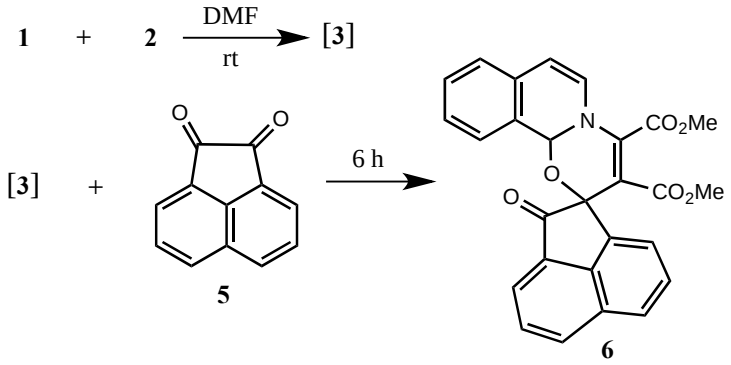
Multicomponent reactions (MCRs) involve the one-pot combination of three or more reactants to afford single products that feature structural elements of all the starting materials, thereby displaying a high degree of synthetic efficiency and atom economy. Because of their modular features, MCRs generate relatively complex products, ideally in one step, amenable to a broad range of substitution patterns.[1,2] The basic principles of 1,4-dipolar cycloaddition reactions, a subclass of MCRs, were provided by the pioneering work of Huisgen.[3] In effect, the pronounced reactivity of aza-heterocycles towards dimethyl acetylenedicarboxylates **2** (DMAD) is well-documented.[3,4] The reaction generally involves nucleophilic addition of the nitrogen atom onto DMAD with consequent formation of 1,4-dipolar intermediate; trapping of the latter zwitterion by suitable dipolarophiles leads to a variety of heterocyclic systems. In

essence, 1,4-dipolar cycloaddition reactions constitute an efficient and versatile process for the construction of six-membered aza-heterocycles.[4] An interesting example of this type is the dipolar zwitterion **3**, generated in situ from isoquinoline **1** and DMAD **2**; the transient existence of **3** was established (by Huisgen *et al.*)[5] via its rapping with diethyl mesooxalate to afford the tricyclic product **4** (Scheme 1).



Scheme 1

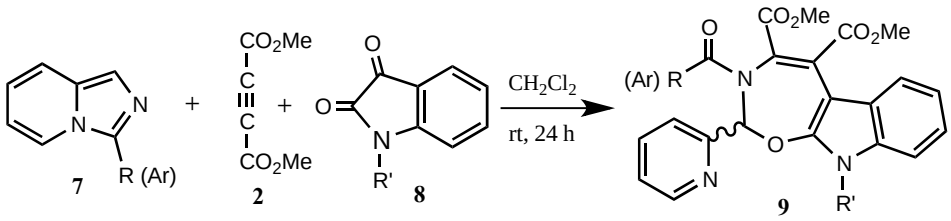
Recently, the dipole **3** was trapped by one keto group of acenaphthene-1,2-dione **5** in a cycloaddition mode to produce the corresponding 2-oxospiro[acenaphthene-[1,3]oxazino[2,3-*a*]isoquinoline derivative **6** (Scheme 2).[6] Parallel results of spiro[1,3]oxazino-cycloadducts were also attained from three-component reactions involving quinoline, DMAD and an assortment of symmetric (e.g. **5**) and other unsymmetric 1,2-quinones.[6,7]



Scheme 2

Seven-membered heterorings fused to aromatic or heteroaromatic nuclei represent highly privileged structures in medicinal chemistry.[8-11] Quite recently, we have reported on a one-pot synthesis of substituted (±)-3,10-dihydro-2*H*-1,3-oxazepino[7,6-*b*]indoles (**9**) *via* 1,4-dipolar cycloaddition reaction involving 3-alkyl(aryl)imidazo[1,5-*a*]pyridines (**7**), DMAD (**2**) and *N*-alkylisatins (**8**) (Scheme 3).[12] We envisioned that employment of arene-*vic*-diones, in placement of isatins **8**, in their reaction with **7** and **2** would follow a parallel path and produce the respective arene-fused dihydro[1,3]oxazepines. This

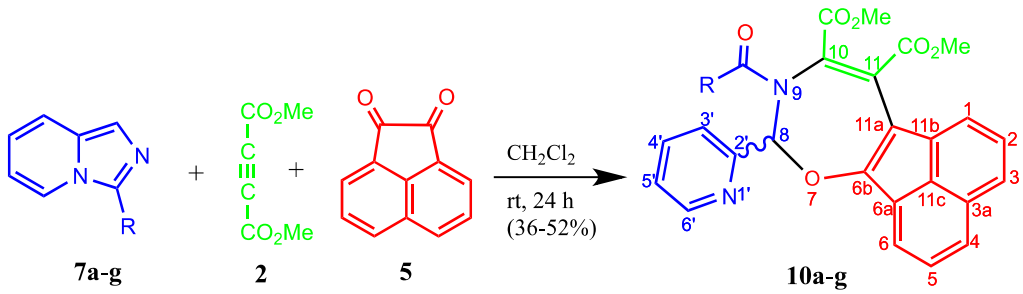
expectation has been realized in the present study which deals with a three-component reaction of **7a-g**, **2** and acenaphthene-1,2-dione **5**, (a representative of symmetrical *o*-quinones), to deliver the respective [*f*]-fused dihydroarene[1,3]oxazepines **10a-g** (Scheme 4, *vide infra*).



Scheme 3

RESULTS AND DISCUSSION

A three-component reaction involving equimolar amounts of the appropriate 3-alkylimidazo[1,5-*a*]pyridine **7a-g**, DMAD **2** and acenaphthene-1,2-dione **5** was performed in dichloromethane at room temperature for 24 h. Work-up of the resulting reaction mixture led in each case to the isolation of an orange-colored solid product which was tentatively assigned the respective acenaphtho[1,2-*f*][1,3]oxazepine structure **10a-g** (Scheme 4).



entry	a	b	c	d	e	f	g
R	Me	Et	^{i}Pr	^{i}Bu	4"-C$_6$H$_4$-1"-CH$_2$	4"-C$_6$H$_4$-1"	Cl-4"-C$_6$H$_4$-1"

Scheme 4

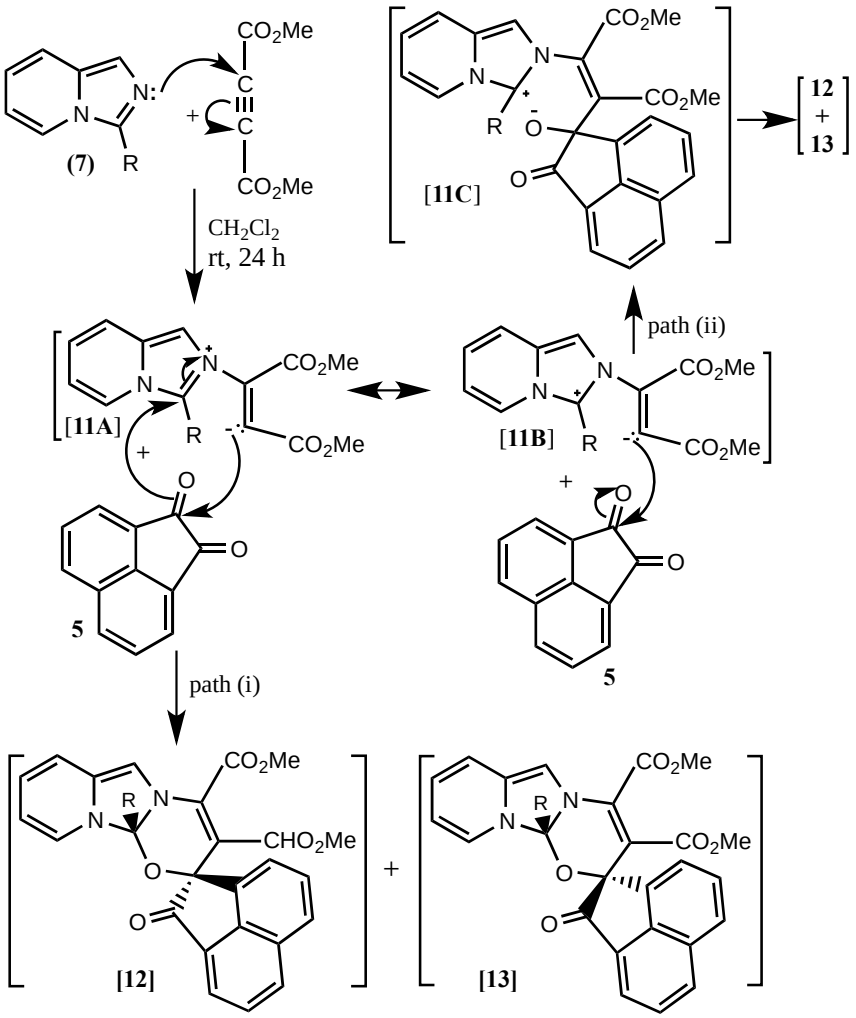
The newly synthesized compounds **10a-g** were characterized by IR, MS and NMR spectral data. These data, detailed in the experimental section, are consistent with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H- and ^{13}C- signal assignments to the different carbons and their attached and/or neighboring hydrogens. The ^{13}C-NMR spectra lack a quaternary (sp^{3}) ^{13}C-signal at about

80 ppm diagnostic of a spiro-carbon in related spiro-oxindoles,[6,7,13] and thus excludes the diasteriomeric spiro[1,3]oxazine structures **12**, **13** (*cf.* Scheme 5, *vide infra*) for the isolated product. Meanwhile, DEPT experiments feature a strong signal around 85 ppm which, by analogy to related systems,[12] is characteristic of the dihydro[1,3]oxazepine structure and is assigned to the sp^3-C(3)*H* stereogenic carbon in **10a-g**. Eventually, structure **10a** (and by inference **10b-g)** is unambiguously confirmed by single-crystal X-ray crystallography (Figure 1 / *vide infra*).

A plausible reaction pathway to account for the formation of acenaphtho[1,2-*f*][1,3]oxazepine (**10a**) is based on the generation of the presumed intermediate diastereomeric spiro-adducts **12**, **13** (Scheme 5) which then suffer skeletal rearrangement to deliver **10a** as depicted in Scheme 6. Just as isoquinoline forms 1,4-dipole with DMAD (**3** / Scheme 1),[6] imidazo[1,5-*a*]pyridine **7a** is expected to form 1,4-dipole of the type **11A↔11B** (Scheme 5). Thus, the initial step entails conjugate addition of the nucleophilic imidazo *N*-2 "nonbridgehead nitrogen" atom to the triple bond of DMAD, followed by cycloaddition of the resulting Huisgen's 1,4-dipole [**11A↔11B**] onto the keto group of acenaphthene-1,2-dione (**5**) to produce the respective transient spiro-1,3-oxazine cycloadducts **12**, **13** (path (i)). However, a two-step process involving the intermediacy of the alkoxide anion [**11C**] (path (ii)) might not be excluded. In turn, the spiro compound **12** (and by inference **13**), incorporating a rather unstable array of three electronegative "*O*, *N*, *N*" atoms at the sp^3 carbon-3, is liable to undergo a cascade of intramolecular π-bond making and consequent σ-bond breaking, producing a resonance-stabilized dipolar ion [**12A↔12B**] (Scheme 6). Among the various conformations of the latter, conformer **12C** embodies the oxyanion and carbocation dipoles situated in such close proximity that allows for their σ-bond formation and subsequent delivery of the respective (±)-acenaphtho[1,2-*f*][1,3]oxazepine derivative **10a**. The domino steps, depicted in Scheme 6, allow for the dihydropyridine ring to restore aromaticity. Likewise, a new *π*-bond formed between C1 and C2 of acenaphthenone part of the spiro adducts **12**, **13**, generates an aromatic acenaphthylene ring system which is in direct conjugation with the maleate moiety. Collectively, these extended *π*-conjugative changes constitute the driving force for the observed conversion of spiroadducts **12**, **13** into the more stable end products **10**. This suggested meachanism is essentially similar to that advanced recently for the production of 1,3-oxazepino[7,6-*b*]indoles **7** in a three component reaction of **9**, **2** and *N*-alkylisatins (*cf.* Scheme 3).[12] As in several instances, chemistry has always new and intriguing surprises in stores.

In this context, It is worth mentioning that dihydro- and tetrahydro-1,3-oxazepines, 1,3-benzoxazepines and heterocycle-fused 1,3-oxazepines are receiving interest due to their important properties and activities in biological systems. Compounds **14-23**, shown in Figure 2, are notable examples of these heterocycles, while their synthesis is achieved by a variety of protocols.[14-23] These 1,3-oxazepines include the naturally

occurring cyclocarbamides **14 A**, **B** isolated from *Steptoverticillium* sp. and evaluated as good plant growth regulators,[14] the pentacyclic **15** which is a *jadomycin* analog[15] containing seven membered E-ring, and the tetracyclic **16** endowed with potential medicinal applications;[16] compound **17**[17] is a 2-thioxo-4,7-dione derivative, **18** and related analogs display liquid crystal properties,[18] **19** exhibits neuropharmacological potency / $GABA_B$ agonist,[19] **20** is a potential inhibitor of glycogen phosphorylase,[20] **21** shows anti-influenza neuraminidase activity,[21] **22** is a *cis* β-lactam fused with hexahydro-1,3-oxazepine,[22] and **23** is a peptidomimetic.[23]

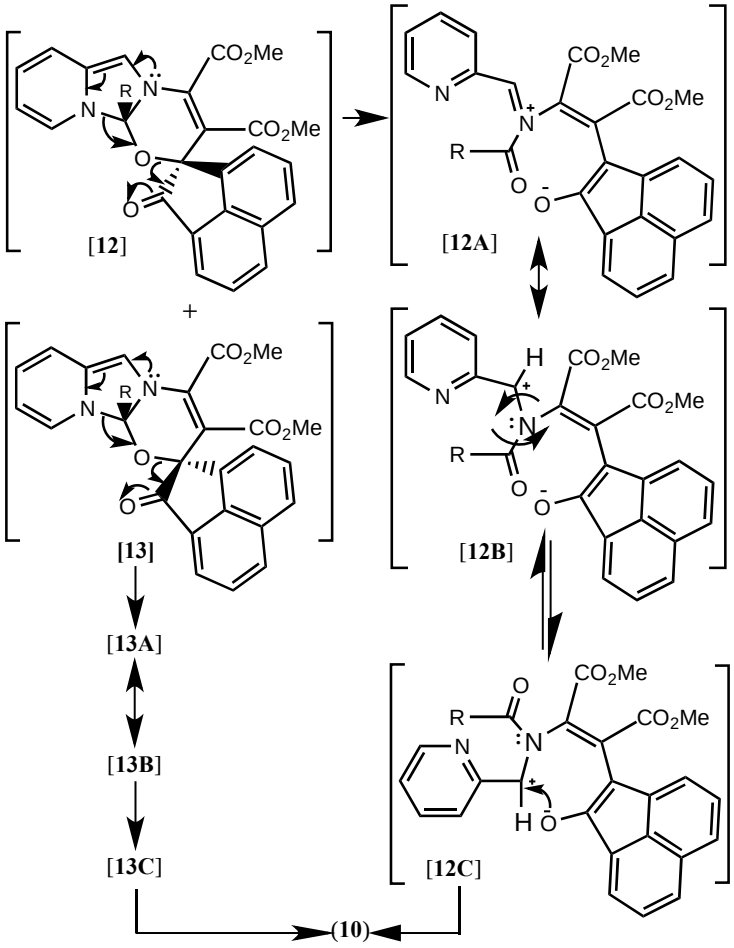


Scheme 5. Postulated mechanism for the formation of the presumed spiro-1,3-oxazine cycloadducts **12**, **13**

X-Ray Structure

An X-ray crystal structure determination was performed to confirm the structure of **10a** (Scheme 5). A summary of data collection and refinement parameters is given in Table 1, while selected bond lengths and angles are provided in Table 2. The molecular structure of **10a**, based on crystallographic data, is displayed

in Figure 1. The seven-membered ring is planar, the mean deviation of the atoms from the plane of the ring is 0.169 Å (the deviation range being 0.011-0.398 Å); atoms N9 and C8 are the most deviated from the plane with respective deviation distances 0.397 and 0.398. The ester carbonyl groups are nearly perpendicular to one another; the angle between the plane of the two carbonyl groups (C11, C25, O26, and O27) and (C10, C21, CO22, and O23) is 86.3°. Similarly, the ester group (C10, C21, CO22, and O23) is nearly perpendicular to the amide group (N9, C18, C19, and O20); the angle between the planes of the two groups is 70.6°. These perpendicular arrangements are stabilized by C(carbonyl)…O interactions as shown in Figure 1. The C(carbonyl)…O distances are significantly shorter than the sum of van der Waals radii, the O22…C25 and O23…C18 distances being 2.6 and 3.00 Å, respectively, which are 0.6 and 0.2 Å less than the sum of van der Waals radii. This pattern has recently been reported in related fused 1,3-oxazepines.[12]



Scheme 6. Proposed mechanism for the rearrangement of the presumed spiro-1,3-adducts **12**, **13** into the respective 1,3-oxazepines **10**

In summary, we have uncovered an unusual one-pot synthesis of acenaphtho[1,2-*f*][1,3]oxazepines. This novel methodology, utilizing various 3-alkyl(aryl)imidazo[1,5-*a*]pyridines in 1,4-dipolar cycloaddition reaction, opens up an easy access to numerous new derivatives which will hopefully facilitate the study of

their chemistry and evaluation of their biological activity. Currently, the scope and limitations of the 1,4-dipolar cycloaddition reaction described here utilizing various imidazo[1,5-*a*]-*N*-heterocycles and other arene-*vic*-diones (*o*-quinones) is underway.

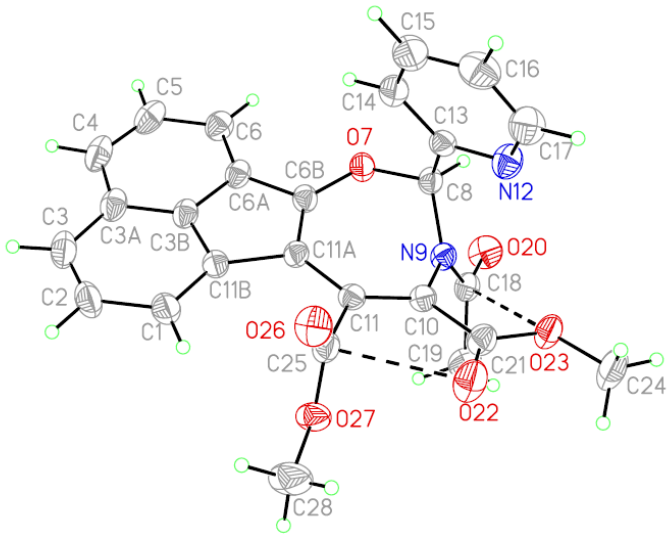


Figure 1. Molecular structure and atom numbering scheme of **10a**. Thermal ellipsoids are drawn at 30% probability level

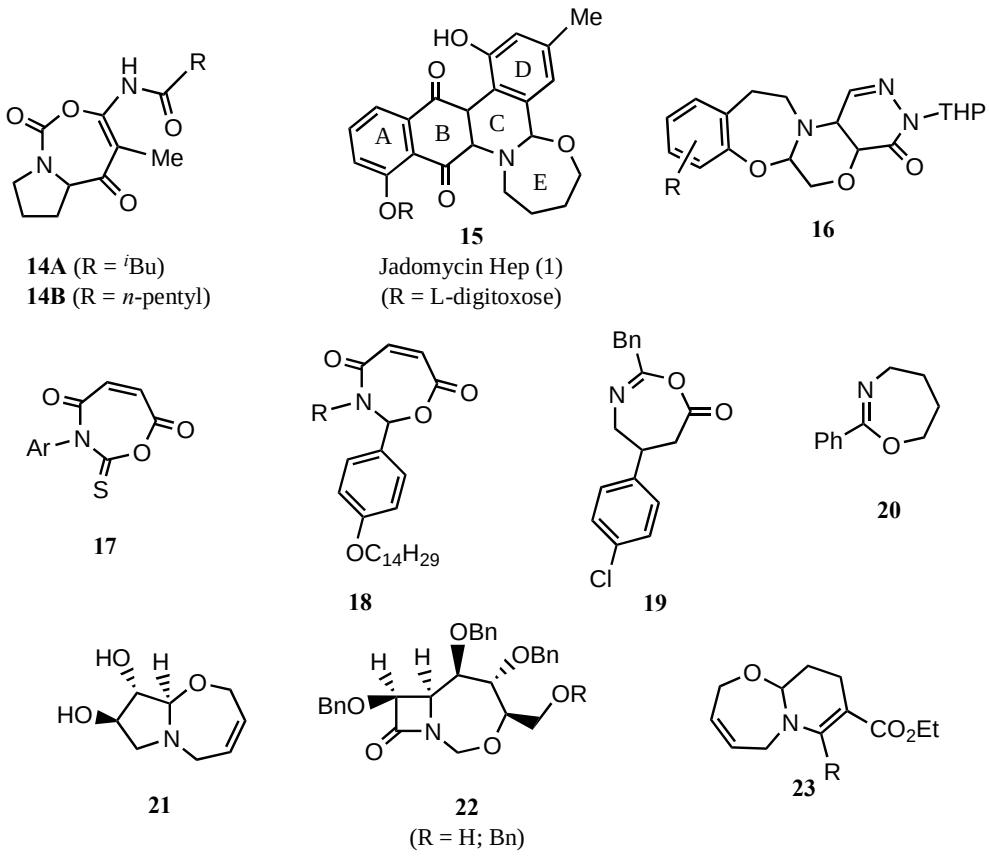


Figure 2. Representatives of monocyclic and condensed 1,3-oxazepines

Table 1. Crystal data and structure refinement for compoud **10a**

Empirical formula	$C_{26}H_{20}N_2O_6$
Formula weight	456.44 g mol^{-1}
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.2267(6) Å
	b = 10.1459(7) Å
	c = 14.0009(10) Å
	α = 82.600(6)°
	β = 77.125(6)°
	γ = 75.472(6)°
Volume	1099.52(14) $Å^3$
Z	2
Density (calculated)	1.379 g cm^{-3}
Absorption coefficient (μ)	0.099 mm^{-1}
F(000)	476
Theta range for data collection	2.99 to 26.30°
Index ranges *hkl*	$-10 \le h \le 10$, $-10 \le k \le 12$, $-17 \le l \le 16$
Reflections collected	8224
Independent reflections	4453 [R_{int} $(F)^2$ = 0.0333]
Completeness to theta = 26.30°	99.8%
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4453 / 0 / 310
Goodness-of-fit on F^2	1.015
Final R indices [$I > 2\ \sigma\ (I)$]	R_1[a] = 0.0545, wR_2[b] = 0.1055
R indices (all data)	R_1[a] = 0.1069, wR_2[b] = 0.1356
Largest diff. peak and hole	0.172 and -0.169 e $Å^{-3}$

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$

[b] $wR_2 = \{\sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2\}^{1/2}$

Table 2. Bond lengths (Å) and angles (deg) for compound **10a**

O(7)-C(8)	1.433(3)	C(6B)-O(7)-C(8)	119.13(17)
N(9)-C(8)	1.451(3)	O(7)-C(8)-C(13)	111.57(18)
N(9)-C(10)	1.420(2)	O(7)-C(8)-N(9)	110.48(19)
C(11)-C(10)	1.353(3)	C(10)-N(9)-C(8)	118.57(17)
C(11)-C(11A)	1.441(3)	C(18)-N(9)-C(8)	118.97(17)
C(11A)-C(11B)	1.495(3)	C(11)-C(10)-N(9)	120.1(2)
C(6B)-C(11A)	1.397(3)	N(9)-C(10)-C(21)	118.9(2)
C(3B)-C(6A)	1.398(3)	C(10)-C(11)-C(11A)	124.7(2)
O(7)-C(6B)	1.349(3)	C(10)-C(11)-C(25)	119.4(2)
C(13)-C(8)	1.516(3)	C(11A)-C(11)-C(25)	115.8(2)
N(9)-C(18)	1.384(3)	C(11)-C(11A)-C(11B)	125.6(2)
O(20)-C(18)	1.213(3)	C(1)-C(11B)-C(11A)	137.3(2)
C(18)-C(19)	1.493(3)	C(6B)-C(11A)-C(11B)	105.58(19)
C(10)-C(21)	1.488(3)	O(7)-C(6B)-C(6A)	117.2(2)
C(11)-C(25)	1.504(3)	O(7)-C(6B)-C(11A)	131.9(2)
C(6B)-C(6A)	1.451(3)	N(9)-C(18)-C(19)	117.9(2)

EXPERIMENTAL

(2-Pyridyl)methylamine, DMAD and acenaphthene-1,2-dione, were purchased from Acros and used as received. Melting points (uncorrected) were determined on a Stuart scientific melting point apparatus in open capillary tubes. IR spectra were measured with a Thermo Nicolet Nexus 670 FT-IR instrument. ^{1}H-, ^{13}C-, and 2D NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III) with TMS as internal standard. Chemical shifts are expressed in δ units; J values for ^{1}H-^{1}H coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were measured (in positive ion mode) using the electrospray ion trap (ESI) technique on a Bruker APEX-IV (7 Tesla) instrument. The samples were dissolved in chloroform and infused using a syringe pump with a flow rate of 2 μL/min. External calibration was conducted using an arginine cluster at a mass range of *m/z* 175-871.

3-Alkyl(aryl)imidazo[1,5-*a*]pyridines (7a-g). 3-Methylimidazo[1,5-*a*]pyridine (**7a**) is prepared from (2-pyridy)methylamine *via* acetylation of the amino group, followed by cyclization of the resulting *N*-acetyl product using phosphorus oxychloride,[24] or *p*-toluenesulfonic acid monohydrate[25] according to

reported procedures.[24,25] The latter procedure[25] is also adopted for the preparation of 3-ethylimidazo[1,5-*a*]pyridine (**7b**), 3-isopropylimidazo[1,5-*a*]pyridine (**7c**) and 3-isobutylimidazo[1,5-*a*]pyridine (**7d**). Compound **7f** is prepared utilizing pyridine-2-carboxaldehyde and (±)-phenylglycine according to a typical reported procedure.[26] This same procedure is also applied for the preparation of **7e** using (±)-phenylalanine, 3-(4-chlorophenyl)imidazo[1,5-*a*]pyridine was prepared from 2-pyridylmethylamine *via* aroylation,[27] followed by cyclization of the resulting caroxamide with phosphorous oxychloride.[24] The NMR data of compounds **7a-g** are identical to those reported in the literature.[28]

General experimental procedure for the synthesis of compounds (10a-g). To a stirred solution of DMAD (0.14 g, 1.0 mmol) and acenaphthene-1,2-dione **5** (0.36 g, 1.0 mmol) in anhydrous $CHCl_3$ (20 mL) was added dropwise the appropriate imidazo[1,5-*a*]pyridine **7** (1.0 mmol) in $CHCl_3$ (5 mL) under argon at rt. For **7a-d**, the reaction mixture was stirred at rt for 24, while for compounds **7e-g** the mixture was heated under reflux for 24 h. The solvent was then removed *in vacuo*, and the residue purified by chromatographic separation on silica gel plates, eluting with *n*-hexane-EtOAc (4:1, v/v). The reaction proceeds equally well in CH_2Cl_2 with **7a-d**.

Dimethyl 9-acetyl-8-(pyridin-2-yl)-8,9-dihydroacenaphtho[1,2-*f*][1,3]oxazepine-10,11-dicarboxylate (10a). Yield: 0.24 g (52%); mp 130-131 ºC. IR (ν_{max}): 3054, 2948, 1721, 1691, 1582, 1491, 1431, 1366, 1240 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.21 (s, 3H, CH_3CON), 3.86 (s, 6H, 2 CO_2CH_3), 7.21 (pseudo t, 1H, H-5'), 7.38 (d, *J* = 7.6 Hz, 1H, H-3'), 7.43 (d, *J* = 7.2 Hz, 1H, H-1), 7.47 (pseudo t, 1H, H-2), 7.69 (pseudo t, 1H, H-4'), 7.70 (pseudo t, 1H, H-5), 7.74 (d, *J* = 8.0, 1H, H-3), 7.99 (s, 1H, H-8), 8.01 (d, *J* = 9.0 Hz, 1H, H-4), 8.08 (d, *J* = 7.0 Hz, 1H, H-6), 8.53 (d, *J* = 4.4 Hz, 1H, H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.8 (CH_3CON), 52.5 (10-CO_2CH_3), 52.7 (11-CO_2CH_3), 85.4 (C-8), 108.3 (C-11a), 121.2 (C-3'), 121.8 (C-1), 123.6 (C-5'), 123.7 (C-6), 124.5 (C-11), 125.7 (C-3), 126.5 (C-11c), 127.8 (C-5), 128.2 (C-3a), 128.4 (C-2), 130.9 (C-4), 132.3 (C-6a), 135.3 (C-11b), 136.8 (C-4'), 139.2 (C-10), 149.4 (C-6'), 153.9 (C-2'), 162.6 (C-6b), 163.4 (11-CO_2Me), 166.4 (10-CO_2Me), 171.3 (*N*-COMe). HRMS (ESI): *m/z* = Calcd: 457.13941 for $C_{26}H_{21}N_2O_6$, $[M + H]^+$, found: 457.13883.

Dimethyl 9-propionyl-8-(pyridin-2-yl)-8,9-dihydroacenaphtho[1,2-*f*][1,3]oxazepine-10,11-dicarboxylate (10b). Yield: 0.23 g (48%); mp 158-160 ºC. IR (ν_{max}): 3067, 2976, 2881, 1740, 1713, 1694, 1580, 1497, 1467, 1432, 1365, 1287, 1222, 1175, 1123, 1059, 1004 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.06 (t, *J* = 7.2 Hz, 3H, CH_3CH_2CO), 2.30, 2.53 (2 m, 2H, $MeCH_2CO$), 3.77 (s, 3H, 11-CO_2CH_3), 3.79 (s, 3H, 10-CO_2CH_3), 7.14 (pseudo t, 1H, H-5'), 7.31 (d, *J* = 7.9 Hz, 1H, H-3'), 7.38 (d, *J* = 6.9 Hz, 1H, H-1), 7.41 (pseudo t, 1H, H-2), 7.53 (pseudo t, 1H, H-4'), 7.63 (pseudo t, 1H, H-5), 7.67 (d, *J* = 7.9, 1H, H-3), 7.93

(d, *J* = 9.0 Hz, 1H, H-4), 7.97 (s, 1H, H-8), 8.02 (d, *J* = 6.8 Hz, 1H, H-6), 8.46 (d, *J* = 3.5 Hz, 1H, H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 9.0 (*C*$H_3$$CH_2$CO*N*), 28.3 (*C*$H_2$CON), 52.5 (11-$CO_2$*C*$H_3$), 52.7 (10-$CO_2$*C*$H_3$), 85.6 (C-8), 108.2 (C-11a), 121.3 (C-3'), 121.7 (C-1), 123.6 (C-5'), 123.7 (C-6), 124.1 (C-11), 125.6 (C-3), 126.5 (C-11c), 127.8 (C-5), 128.2 (C-3a), 128.4 (C-2), 130.8 (C-4), 132.4 (C-6a), 135.4 (C-11b), 136.8 (C-4'), 139.4 (C-10), 149.3 (C-6'), 154.0 (C-2'), 162.6 (C-6b), 163.5 (11-*C*O_2Me), 166.5 (10-*C*O_2Me), 174.7 (*N*-*C*OEt). HRMS (ESI): *m/z* = Calcd: 493.13701 for $C_{27}H_{22}N_2O_6Na$, $[M + Na]^+$, found: 493.13750.

Dimethyl 9-isobutyryl-8-(pyridin-2-yl)-8,9-dihydroacenaphtho[1,2-*f*][1,3]oxazepine-10,11-dicarboxylate (10c). Yield: 0.22 g (45%); mp 189-190 °C. IR (ν_{max}): 3060, 2975, 2880, 1739, 1716, 1686, 1588, 1467, 1430, 1363, 1327, 1243, 1288, 1122, 1092, 1062, 1003 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.86, 1.18 (2d, *J* = 6.5 Hz, 6H, (C*H*$_3$)$_2$CHCO), 2.75 (m, 1H, (Me)$_2$C*H*CO), 3.79 (s, 3H, 11-CO_2CH_3), 3.80 (s, 3H, 10-CO_2CH_3), 7.15 (pseudo t, 1H, H-5'), 7.32 (d, *J* = 7.8 Hz, 1H, H-3'), 7.38 (d, *J* = 6.9 Hz, 1H, H-1), 7.42 (pseudo t, 1H, H-2), 7.53 (pseudo t, 1H, H-4'), 7.65 (pseudo t, 1H, H-5), 7.69 (d, *J* = 8.0, 1H, H-3), 7.94 (d, *J* = 8.1 Hz, 1H, H-4), 7.98 (s, 1H, H-8), 8.02 (d, *J* = 6.9 Hz, 1H, H-6), 8.47 (d, *J* = 3.1 Hz, 1H, H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 18.1, 20.8 (*C*H_3)$_2$CHCO*N*), 34.7 (*C*HCON), 52.6 (11-CO_2*C*H_3), 52.7 (10-CO_2*C*H_3), 85.1 (C-8), 108.4 (C-11a), 121.3 (C-3'), 121.7 (C-1), 123.5 (C-5'), 123.6 (C-6), 124.0 (C-11), 125.6 (C-3), 126.5 (C-11c), 127.8 (C-5), 128.3 (C-3a), 128.4 (C-2), 130.7 (C-4), 132.4 (C-6a), 135.4 (C-11b), 136.8 (C-4'), 138.6 (C-10), 149.1 (C-6'), 154.0 (C-2'), 162.1 (C-6b), 163.6 (11-*C*O_2Me), 166.5 (10-*C*O_2Me), 178.4 (*N*-*C*OCH(Me)$_2$). HRMS (ESI): *m/z* = Calcd: 507.15266 for $C_{28}H_{24}N_2O_6Na$, $[M + Na]^+$, found: 507.15173; calcd: 991.31609 for $C_{56}H_{48}N_4O_{12}Na$, $[2M + Na]^+$, found: 991.31444.

Dimethyl 9-(3-methylbutanoyl)-8-(pyridin-2-yl)-8,9-dihydroacenaphtho[1,2-*f*][1,3]oxazepine-10,11-dicarboxylate (10d). Yield: 0.22 g (44%); mp 166-168 °C. IR (ν_{max}): 3057, 2953, 2924, 2864, 1735, 1714, 1685, 1580, 1492, 1466, 1430, 1368, 1286, 1201, 1120, 1063, 1003 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.73, 0.93 (2d, *J* = 6.6 Hz, 6H, (C*H*$_3$)$_2$CHCH$_2$), 2.17 (m, 1H, (Me)$_2$C*H*CH$_2$), 2.25 (dd, *J* = 7.1 Hz, 15.2 Hz, 2H, C*H*$_A$H$_B$ / C*H*$_2$CO), 2.40 (dd, *J* = 6.5 Hz, 15.2 Hz, IH, CH$_A$*H*$_B$ / C*H*$_2$CO), 3.50 (s, 6H, 2CO_2CH_3), 7.21 (dd, *J* = 4.3 Hz, 7.2 Hz, IH, H-5'), 7.37 (d, *J* = 7.9 Hz, 1H, H-3'), 7.44 (d, *J* = 7.0 Hz, 1H, H-1), 7.47 (pseudo t, 1H, H-2), 7.59 (m, 1H, H-4'), 7.70 (pseudo t, 1H, H-5), 7.74 (d, *J* = 8.0, 1H, H-3), 8.00 (d, *J* = 8.1 Hz, 1H, H-4), 8.04 (s, 1H, H-8), 8.08 (d, *J* = 7.0 Hz, 1H, H-6), 8.53 (d, *J* = 4.3 Hz, 1H, H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 22.1, 22.6 (*C*H_3)$_2$CHCH$_2$), 25.4 (*C*H(Me)$_2$), 44.0 (*C*H_2CON), 52.5 (11-CO_2*C*H_3), 52.7 (10-CO_2*C*H_3), 85.3 (C-8), 108.5 (C-11a), 121.2 (C-3'), 121.7 (C-1), 123.5 (C-5'), 123.6 (C-6), 124.3 (C-11), 125.6 (C-3), 126.5 (C-11c), 127.8 (C-5), 128.2 (C-3a), 128.4 (C-2), 130.8, (C-4), 132.3 (C-6a), 135.3 (C-11b), 136.8 (C-4'), 139.0 (C-10), 149.3 (C-6'), 154.1 (C-2'), 162.4 (C-6b), 163.4 (11-*C*O_2Me), 166.5 (10-*C*O_2Me), 173.5 (*N*-*C*OCH(Me)$_2$). HRMS (ESI): *m/z* = Calcd: 521.16831

for $C_{29}H_{26}N_2O_6$ Na, $[M + Na]^+$, found: 521.17028.

Dimethyl 9-(2-phenylacetyl)-8-(pyridin-2-yl)-8,9-dihydroacenaphtho[1,2-*f*][1,3]oxazepine-10,11-dicarboxylate (10e). Yield: 0.22 g (42%); mp 92-94 ºC. IR (ν_{max}): 3027, 2954, 2920, 2850, 1736, 1715, 1687, 1582, 1492, 1463, 1234, 1207, 1197, 1120, 1065, 1002 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.76, 3.87 (AB system, *J* = 15.4 Hz, 2H, H_ACH_B-Ph), 3.84 (s, 6H, $2CO_2CH_3$), 6.87 (t, *J* = 7.4 Hz, 1H, H-4″), 6.96 (pseudo t, 2H, H-3" / H-5"), 7.15 (d, *J* = 7.5 Hz, 2H, H-2" / H-6"), 7.21 (pseudo t, 1H, H-5'), 7.31 (d, *J* = 7.1 Hz, 1H, H-3'), 7.36 (d, *J* = 8.0 Hz, 1H, H-1), 7.45 (pseudo t, 1H, H-2), 7.60 (pseudo t, 1H, H-4'), 7.68 (pseudo t, 1H, H-5), 7.73 (d, *J* = 8.3, 1H, H-3), 7.99 (d, *J* = 8.2 Hz, 1H, H-4), 8.02 (s, 1H, H-8), 8.03 (d, *J* = 7.0 Hz, 1H, H-6), 8.45 (d, *J* = 4.5 Hz, 1H, H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 42.3 (CH_2-Ph), 52.6 (10-CO_2CH_3), 52.7 (11-CO_2CH_3), 85.9 (C-8), 108.6 (C-11a), 121.3 (C-1), 121.8 (C-3'), 123.5 (C-5'), 123.6 (C-6), 124.1 (C-11), 125.5 (C-3), 126.4 (C-11c), 126.5 (C-4"), 127.7 (C-5), 128.1 (C-3" / C-5"), 128.2 (C-3a), 128.3 (C-2), 129.2 (C-2" / C-6"), 130.7 (C-4), 132.2 (C-6a), 133.8 (C-1"), 135.3 (C-11b), 136.8 (C-4'), 139.6 (C-10), 149.4 (C-6'), 153.9 (C-2'), 162.5 (C-6b), 163.5 (11-CO_2Me), 166.3 (10-CO_2Me), 172.1 (*N*-COBz). HRMS (ESI): *m/z* = Calcd: 533.17071 for $C_{32}H_{25}N_2O_6$, $[M+H]^+$, found: 533.17043; calcd: 555.15266 for $C_{32}H_{24}N_2O_6Na$, $[M+Na]^+$, found: 555.15311.

Dimethyl 9-(2-benzoyl)-8-(pyridin-2-yl)-8,9-dihydroacenaphtho[1,2-*f*][1,3]oxazepin-10,11-dicarboxylate (10f). Yield: 0.19 g (36%); mp 150-152 ºC. IR (ν_{max}) 3060, 2960, 2918, 2850, 1742, 1715, 1674, 1578, 1492, 1464, 1430, 1370, 1257, 1228, 1146, 1120, 1065, 1007 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.50 (s, 3H, 10-CO_2CH_3), 3.81 (s, 3H, 11-CO_2CH_3), 7.19 (pseudo t, 1H, H-5'), 7.33 (pseudo t, 2H, H-3" / H-5"), 7.41 (d, *J* = 7.0 Hz, 1H, H-4"), 7.42 (d, *J* = 7.6 Hz, 1H, H-3'), 7.51 (pseudo t, 1H, H-2), 7.54 (d, *J* = 7.1 Hz, 1H, H-1), 7.58 (pseudo t, 1H, H-4'), 7.59 (d, *J* = 7.4 Hz, 2H, H-2" / H-6"), 7.74 (pseudo t, 1H, H-5), 7.79 (d, *J* = 7.5, 1H, H-3), 8.03 (d, *J* = 7.5 Hz, 1H, H-4), 8.13 (d, *J* = 8.0 Hz, 1H, H-6), 8.34 (s, 1H, H-8), 8.52 (d, *J* = 3.2 Hz, 1H, H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 52.0 (10-CO_2CH_3), 52.6 (11-CO_2CH_3), 84.8 (C-8), 109.0 (C-11a), 121.3 (C-3'), 122.3 (C-1), 123.4 (C-5'), 123.5 (C-6), 125.8 (C-3), 125.9 (C-11), 126.5 (C-11c), 127.9 (C-3" / C-5"), 128.0 (C-5), 128.2 (C-2" / C-6"), 128.3 (C-3a), 128.5 (C-2), 130.8 (C-4), 131.2 (C-4"), 132.4 (C-6a), 135.3 (C-11b), 135.7 (C-1"), 135.9 (C-10), 136.7 (C-4'), 149.4 (C-6'), 153.8 (C-2'), 162.8 (10-CO_2Me), 162.9 (C-6b), 166.5 (11-CO_2Me), 170.4 (*N*-COPh). HRMS (ESI): *m/z* = Calcd: 519.15506 for $C_{31}H_{23}N_2O_6$, $[M+H]^+$, found: 519.15598.

Dimethyl 9-[2-(4-chlorobenzoyl)-8-(pyridin-2-yl)-8,9-dihydroacenaphtho[1,2-*f*][1,3]oxazepine-10,11-dicarboxylate (10g). Yield: 0.24 g (46%); mp 115-117 ºC. IR (ν_{max}): 3067, 3017, 2950, 2914, 2844, 1742, 1716, 1674, 1586, 1490, 1430, 1368, 1282, 1257, 1141, 1090, 1063, 1009 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.54 (s, 3H, 11-CO_2CH_3), 3.83 (s, 3H, 10-CO_2CH_3), 7.18 (pseudo t, 1H, H-5'), 7.32 (d, *J* = 8.0 Hz,

2H, H-3" / H-5"), 7.41(d, *J* = 7.8 Hz, 1H, H-3'), 7.52 (d, *J* = 7.0 Hz, 1H, H-1), 7.53 (pseudo t, 1H, H-2), 7.53 (d, *J* = 8.0 Hz, 2H, H-2" / H-6"), 7.59 (pseudo t, 1H, H-4'), 7.74 (pseudo t, 1H, H-5), 7.79 (pseudo t,1H, H-3), 8.04 (d, *J* = 8.1 Hz, 1H, H-4), 8.13 (d, *J* = 6.7 Hz, 1H, H-6), 8.31 (s, 1H, H-8), 8.52 (d, *J* = 3.4 Hz, 1H, H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 52.1 (11-CO_2CH_3), 52.7 (10-CO_2CH_3), 84.8 (C-8), 108.9 (C-11a), 122.3 (C-3'), 122.8 (C-1), 123.5 (C-5'), 123.6 (C-6), 125.6 (C-11), 125.9 (C-3), 126.5 (C-11c), 127.9 (C-5), 128.3 (C-3a), 128.4 (C-2), 131.0 (C-4), 132.3 (C-6a), 135.1 (C-11b), 136.8 (C-4'), 137.4 (C-10), 149.5 (C-6'), 153.6 (C-2'), 163.0 (C-6b), 162.7 (11-CO_2Me), 166.4 (10-CO_2Me), 169.4 (*N*-COMe), 128.5 (C-3" / C-5"), 129.5 (C-2" / C-6"), 132.9 (C-9a), 134.2 (C-1"), 137.3 (C-4"). HRMS (ESI): *m/z* = Calcd: 575.09804 for $C_{31}H_{21}{}^{35}ClN_2O_6Na$, $[M+Na]^+$, found: 575.09847; calcd: 577.09673 for $C_{31}H_{21}{}^{37}ClN_2O_6Na$, $[M+2+Na]^+$, found: 577.09640.

X-Ray structure analysis of compound 10a. Crystals were grown by slow evaporation of a dilute solution of **10a** in dichloromethane. The title compound crystallized out as rhombic deep orange crystals. A suitable crystal, with approximate dimensions of 0.4 × 0.2 × 0.1 mm, was epoxy-mounted on a glass fiber. Data were collected at room temperature (293 K) using an Oxford Xcalibur diffractometer. Data were acquired and processed to give SHELX-format-*hkl* files using CrysAlisPro software.[29] Cell parameters were determined and refined using CrysAlisPro.[29] A multiscan absorption collection was applied with maximum and minimum transmission factors of 1.00000 and 0.82810, respectively. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using all unique data.[30] All nonhydrogen atoms were refined anisotropically with the hydrogen atoms placed on the calculated positions using riding model.

Crystallographic data for the structural analysis of **10a** have been deposited with the Cambridge Crystallographic Data Center under the depository No. 1563051. Copies of information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44-1223-336033; e-mail: (deposit@ccdc.com.ac.uk or http://www.ccdc.ac.uk).

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