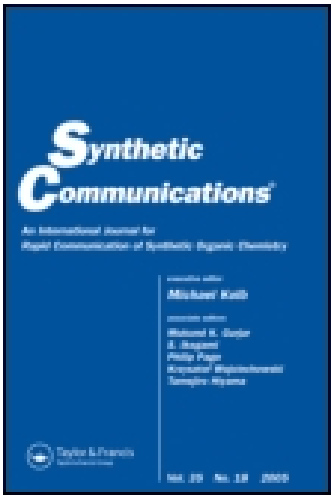

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Regioselective Condensation of Alkylidenephosphoranes to N-Methoxy- and N-Anilino-1H isoindole-1,3-(2H)-diones

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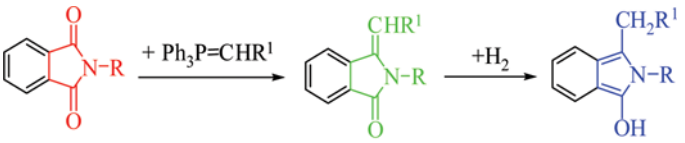
REGIOSELECTIVE CONDENSATION OF ALKYLIDENEPHOSPHORANES TO *N*-METHOXY- AND *N*-ANILINO-1*H* ISOINDOLE-1,3-(2*H*)-DIONES

Wafaa M. Abdou, Rizk E. Khidre, and Reham F. Barghash
Chemical Industries Division, National Research Centre, Giza, Egypt

GRAPHICAL ABSTRACT



68-78%

R = OMe, NHPh
R^1 = CO_2Me, R^1 = CO_2Et, R^1 = COMe, R^1 = COPh, R^1 = CN

Abstract *Treatment of 2-methoxyisoindoline-1,3-dione with resonance-stabilized alkylidenephosphoranes afforded the corresponding monoalkenes as the sole reaction product, in ~58–63% yields, whereas more than 80% yields of the same monoolefin products were obtained when the reactions were carried out under microwave conditions. Similarly, 2-(phenylamino)isoindoline-1,3-dione reacted under either thermal or microwave conditions to give only the corresponding monoalkene derivatives. The alkene products from both substrates were further reduced to the corresponding isoindoles using Zn-dust in EtOH. Prediction of the designed compounds and the in vivo anti-inflammation activity of the products in the rat adjuvant model were also studied. The work is the first demonstration of the anti-inflammatory activity of phthalimide derivatives.*

Keywords Alkylidenephosphoranes; inflammatory inhibition; *N*-substituted phthalimides; olefination

INTRODUCTION

For many years, phthalimides have been a focus of interest as an important class of organic compounds with medicinal and biological importance.[1–8] We have precedently described synthesis of various phthalimidophosphor derivatives, and thus α-aminophosphates, amido-phosphates, and oxoazirdin-1-yl-phosphonic diamide were prepared by applying different types of P(III) reagents **5a-c** to *N*-phthaloylalanylazide (**3**).[9] The study was extended to the application of some Wittig

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reagents **4a-e** on **3**, giving the corresponding linear disubstituted 1,2,3-triazoles.[9] Later on,[10] we showed that *N*-methoxy- (**1**) of *N*-anilinophthalimide (**2**) behave differently toward trialkyl phosphites **5a**, dialkylphosphonates **5b**, and tris(dialkyl-amino)phosphines **5c**, and thereby the respective α-aminophosphonates, amido-phosphonates, phosphonic acid diamides, and oxadiazaphospholes were successfully obtained. The main feature of all reactions investigated in the two articles[9,10] is the nucleophilic attack on the 2-*N*-substituents in **1**, **2**, and **3** by the P(III) **5** and P(V) **4** reagents. On the basis of bioassay results, some of products from the previous two articles could be considered as lead molecules to be modified in order to improve their antibiotic properties. Continuing our research work on phthalimides and related phosphor derivatives, we herein envisage the importance of the nature of substituents on the nitrogen atom in isoindole-1,3(*2H*)-diones **1**, **2**, and **3** on their reactivity toward Wittig reagents **4a-e**. Different behaviors were observed between **1** or **2** and *N*-phthaloyl-alanylazide (**3**), notably in the susceptibility of nucleophilic attack by alkylidenephosphoranes on the 1,3-carbonyl-carbon. The computer-assisted molecular modeling (CAMM) PASS program was adopted for designing—in silico—the structures of potentially active molecules for future synthesis. Later on, the in vivo activity of the synthesized phthalimides in the rat adjuvant model was also studied in terms of structure–activity relationship (SAR). See Fig. 1.

RESULTS AND DISCUSSION

The behavior of stabilized phosphonium ylides **4a-e** toward 2-methoxy-*1H*-isoindole-1,3-(*2H*)-dione (**1**) was examined to determine the site of attack. Treatment of **1** with an equivalent amount of alkylidene(triphenyl)phosphoranes, namely methoxycarbonylmethylene (**4a**), ethoxycarbonyl-methylene (**4b**), acetylmthylene (**4c**), benzoyl-methylene **4d**, and cyano-methylenetriphenyl-phosphorane (**4e**) in dry boiling toluene containing a few drops (~0.4 mL) of triethylamine (Et_3N) over a period of ≈25 h (monitored by thin-layer chromatography, TLC) afforded the respective monoalkene products **6a–e** (58–63% yield) as the sole reaction products. The same results were obtained whether 1 or 2 equiv of the Wittig reagent was employed. Elemental analyses, infrared (IR), and ^1H and ^{13}C NMR spectra as well as mass spectrometry[11] were the reasons for structure **6** assignments. It is worth mentioning here that even though compounds **6a–c** could be present in *Z* and /or *E*-configuration, they are only

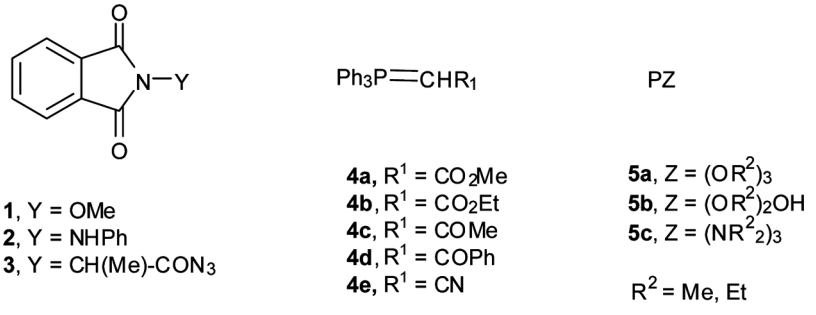


Figure 1. Starting substrates **1–3** and reagents **4a–c** and **5a–c**.

Table 1. Reactions of the substrates **1** and **2** with Wittig reagents **4** under different conditions

Entry	R_1	Conditions	Time	Products	Yield (%)	Mp (°C)
1 + **4a**	CO_2Me	Et_3N/toluene/Δ	30 h	**6a** (*E*-isomer)	58	123–125 (cyclohexane)
1 + **4a**	CO_2Me	DMSO/microwave oven	8 min	**6a** (*E*-isomer)	84	
1 + **4b**	CO_2Et	Et_3N/toluene/Δ	30 h	**6b** (*E*-isomer)	62	128–130 (cyclohexane)
1 + **4b**	CO_2Et	DMSO/microwave oven	8 min	**6b** (*E*-isomer)	85	
1 + **4c**	COMe	Et_3N/toluene/Δ	40 h	**6c** (*E*-isomer)	53	134–136 (Me_2Cl_2)
1 + **4c**	COMe	DMSO/Microwave oven	10 min	**6c** (*E*-isomer)	82	
1 + **4d**	COPh	Et_3N/toluene/Δ	40 h	**6d** (*E*-isomer)	60	120–122 (MeCN)
1 + **4d**	COPh	DMSO/microwave oven	12 min	**6d** (*E*-isomer)	80	
1 + **4e**	CN	Et_3N/toluene/Δ	48 h	**6e** (*E*-isomer)	63	178–180 (EtOH)
1 + **4e**	CN	DMSO/microwave oven	12 min	**6e** (*E*-isomer)	87	
2 + **4a**	CO_2Me	Et_3N/toluene/Δ	22 h	**8a** (*E*-isomer)	58	213–215 (acetone)
2 + **4a**	CO_2Me	DMSO/M microwave oven	10 min	**8a** (*E*-isomer)	82	
2 + **4b**	CO_2Et	Et_3N/toluene/Δ	20 h	**8b** (*E*-isomer)	62	175–177 ($CHCl_3$)
2 + **4b**	CO_2Et	DMSO/microwave oven	10 min	**8b** (*E*-isomer)	85	

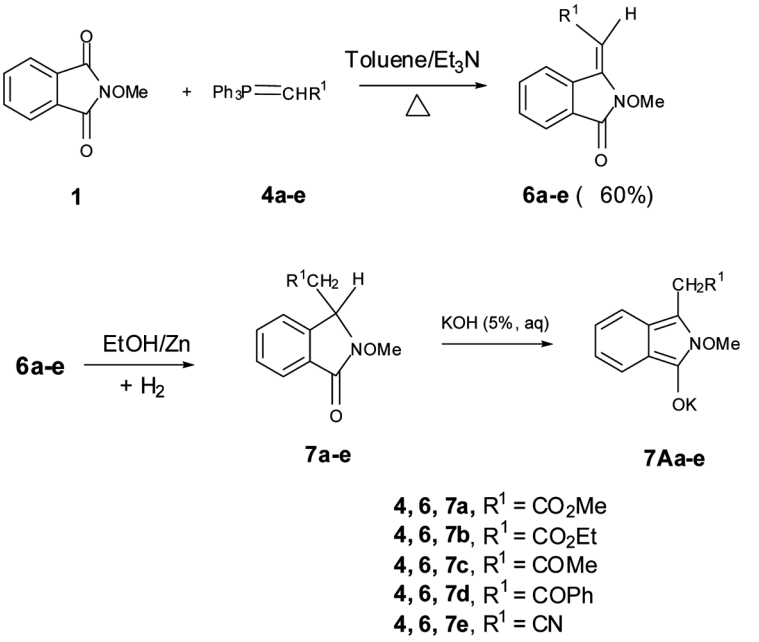
obtained in the *E*-form. In favor of this conclusion are the facts that compounds **6** have sharp melting points and did not show any isomerism in the spectroscopic data, and it is generally accepted that the geometry of the double bond resulted from olefination Wittig reactions of stabilized ylides that have electron-withdrawing groups (CO_2R, COR, CN) is usually *E*. Frequently the *Z*-alkenes having neighboring electron-withdrawing group isomerize to the thermodynamically more stable *E*-isomers.[12–14]

The enormous growth in the use of microwave irradiation in synthetic organic chemistry inspired us to perform the same reactions (**1** + **4a–e**) to achieve, under microwave conditions, significantly remarkable rate enhancement and drastic reduction of the reaction time. Thus, when the substrate **1** and the phosphoranes **4a–e** were mixed in dimethylsulfoxide (DMSO) solution and heated in a microwave oven (1000 W), the olefins **6a–e** were obtained after the usual workup ($\geq 82\%$) in 8–12 min and in the absence of a base (see Table 1).

Similar sequences were applied to another *N*-substituted isoindoline-1,3-dione for obtaining more derivatives of phthalimides like **8a** and **8b** via applying the Wittig reagents **4a** and **4b** on the parent 2-(phenylamino)isoindoline-1,3-dione (**2**) under either thermal or microwave conditions (see Table 1). Compounds **8a,b** were assigned to the *E*-isomer for the same reasons as for compounds **6**.

On the other hand, no reaction was observed when compound **2** was caused to react with either the keto ylides (**4c, 4d**) or cyanomethylenetriphenylphosphorane (**4e**). This behavior is in line with the fact that ketones react sluggishly or not at all with Wittig reagents (stabilized with an acetyl, benzoyl, or cyno group).[13–17]

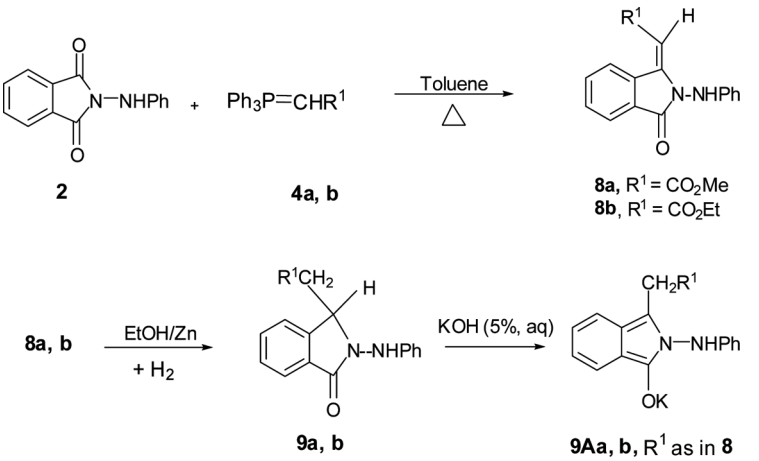
As the bioassay results have identified impressively distinct therapeutic characteristics from potassium salts to the olefin counterparts, reduction of the synthesized olefins was undertaken by treating **6a–e** and **8a,b** with Zn dust in ethanol to give the corresponding reduced forms **7a–e** and **9a,b**, respectively. Compounds **7** and **9** (*E*-isomers) were obtained in the expected much more stable isoindolin-1-ones form. Treating the latter compounds with aqueous solution of KOH (5%) afforded the potassium salt **9Aa**, **9Ab** and **7Aa** and **7Ab** (Schemes 1 and 2).



Scheme 1. Reaction of 2-methoxy-1H-isoindole-1,3-(2H)-dione **1** with Wittig reagents **4a–e**.

Prediction

Prediction of anti-inflammatory activity was made at the earlier stage of the designed series **6a–e**, **7Aa–e**, **8a,b**, and **9Aa,b** using PASS software.[18,19] The prediction result are expressed (**) in Table 2 with appropriate *Pa* and *Pi*, which are the estimates of probability to be active and inactive, respectively. The data in Table 2



Scheme 2. Reaction of N-anilino-1H-isoindole-1,3-(2H)-dione **2** with Wittig reagents **4a,b**.

Table 2. Anti-inflammatory activity of phthalimide derivatives **6a,c**, **7Aa–e**, **8a,b**, and **9Aa,b** in acute carrageenin-induced paw edema in rats

Compound	Mean swelling[a] vol. (mL)	Inhibition of edema %	Potency (%)
Control	0.688	00.0	—
A[b]	0.272	60***[c]	1.00
6a	0.574	16.6***	0.28
6b	0.578	16.8***	0.29
6c	0.566	17.7***	0.30
6d	0.576	14.7***	0.30
6e	0.570	12.7***	0.23
7Aa	0.278	59.6*	0.99*
7Ab	0.377	57.3*	0.95
7Ac	0.348	49.4**	0.82
7Ad	0.376	45.3***	0.76
7Ae	0.381	44.6**	0.74
8a	0.488	29.0**	0.48
8b	0.476	30.8	0.51
9Aa	0.189	71.2*	1.19*
9Ab	0.206	70.1*	1.17*

[a]Data are means of at least two independent determinations with 6 animals in each group (in a dose of 50 mg/kg body weight), and the deviation in absorbance values was less than 10%.

[b]**A** = Indomethacin (used as a reference standard).

[c](SEM: standard error of the mean) statistical significance of results was established using the Student's t-test (***) $P < 0.001$; (**) $P < 0.01$; (*) $P < 0.05$. The anti-inflammatory activity (*prediction results* $^{*} > ^{**} > ^{***}$) was expressed as percentage inhibition of edema volume in treated animals in comparison with the control group as described in the experimental section.

demonstrates that PASS program[19] has proved 100% accurate in its predictions between predicted values and experimental results of anti-inflammatory properties of the tested compounds (i.e., the calculated *Pa* value is proportional to the potency of the compound).

Anti-Inflammatory Activity Screening

The anti-inflammatory activity in vivo of the prepared phthalimide derivatives **6a–e**, **7Aa–e**, **8a,b**, and **9Aa,b** was determined. Respectively, mice were surgically implanted with the acute carrageenin-induced paw edema (CPE) standard method.[20] The anti-inflammatory property of the examined compounds at 50 mg/Kg body weight is shown in comparison with that of indomethacin (**A**), in a dose of 50 mg/kg body weight which used as a reference standard, and the results are collected in Table 2.

Compounds **7Aa** and **7Ab** both significantly inhibited the granuloma at the same dose (50 mg/kg) as the reference, while **9Aa** and **9Ab** exerted the most significant inhibition, which was not dose-related, over the same ranges. Compound **7Ac** showed only moderate activity against the carrageenin granuloma at the same dose, whereas other products showed only low potency.

Finally, the reported activity in vivo in the carrageenin granuloma is the first demonstration of the anti-inflammatory activity of phthalimide derivatives.

Toxicity

In acute toxicity experiments, the in vivo compounds were endowed with a 50% lethal dose of >0.3 mmol/Kg body weight. Thus, toxicological studies of **7Aa,b**, **9Aa**, and **9Ab** were performed using the LD_{50} standard method[21] in mice in 500, 750, and 1000 mg/Kg (body weight), that is, 10–20 folds of the used anti-inflammatory effective dose. However, no toxic symptoms or mortality rates were observed after 24 h postadministration, demonstrating the safe behavior of the doses.

CONCLUSION

The studied reactions in the previous[9,10] and the present investigations are offered as easy ways to transform easily available starting materials into a variety of phthalimide derivatives in satisfactory yields. In addition, our protocol demonstrates an efficient site-selective method for making novel products in good yields from *N*-substituted phthalimides with P(III) and P(V) reagents. In parallel, screening results showed that the potassium salts of phthalimide derivatives **9Aa** and **9Ab** would be good candidates for lead molecules to be modified to improve inflammatory inhibition. Six from 14 compounds tested with carrageenin-induced rat paw edema were found to be potent anti-inflammatory agents (59.7–87.6%). For most of these activities, the presence of a saturated substituent moiety and a hydroxyl group in addition to the phthalimide core seemed to be essential to generate new derivatives with greater anti-inflammatory activity.

EXPERIMENTAL

Melting points were measured on an Electrothermal melting-point apparatus. The IR spectra were recorded on a Perkin-Elmer 317 Grating IR spectrophotometer using KBr pellets. NMR spectra were measured with a Jeol ECA 500-MHz (^{13}C: 125, ^{1}H: 500, ^{31}P: 200 MHz) spectrometer. ^{31}P NMR spectra were recorded with H_3PO_4 (85%) as external reference. ^{1}H and ^{13}C NMR spectra were recorded with trimethylsilane as internal standard in $CDCl_3$ or DMSO-d^6. Chemical shifts (δ) are given in parts per million (ppm). Mass spectra were performed at 70 eV on an MS-50 Kratos (AEI) spectrometer provided with a data system. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. The appropriate precautions in handling moisture-sensitive compounds were considered. TLC: Merck 0.2-mm silica gel 60 F154 aluminum plates. Column chromatography (CC): silica gel (Kieselgel 60 mesh, particle size 0.2–0.5 mm; E. Merck, Darmstadt).

Reaction of *N*-Methoxyphthalimide (1) with Wittig Reagents 4a–e: Synthesis of 6a–e

Under thermal conditions general procedure A. A mixture of alkoxycarbonylmethylene-**4a** (or **4b**), acetylmethylene **4c**, benzoylmethylene **4d**, or cyanomethylene(triphenyl)-phosphine (**4e**) (8.6 mmol) and **1** (1.5 g, 8.5 mmol) in dry toluene (40 mL) containing triethylamine (TEA) (0.5 mL) was heated under

reflux for ≅25 h. After removal of the solvent, the residue was chromatographed on silica gel using *n*-hexane/$CHCl_3$ as eluents to give the respective olefins **6a-e** (Table 1). Triphenylphosphine oxide (TPPO) was isolated (6:4 v/v) and identified from all described reactions.

Methyl 2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate (6a). IR (KBr): $\tilde{\nu} = 1733$, 1713 (C=O, cyclicimide & ester), 1636 (C=C, olefin) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): $\delta = 3.73$ (s, 3H, MeO, ester), 3.94 (s, 3H, *Me*ON), 5.98 (s, 1H, =CH, olefin), 7.76, 7.87 (2d, $J_{H\text{-}H} = 6.8$ Hz, $2 \times 2H$, *H*-Ar) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 170.2$ (C=O, ester), 168.3 (C=O, imide), 146.9 [C(1)], 138.7, 135.2, 127.8, 126.1, 125.8, 125.2 (C-Ar), 86.6 (=*C*H), 62.4 (*Me*ON), 52.3 (O*Me*, ester) ppm; MS (EI, 70 eV): *m/z* (%) = 233 (100) [M^+], 203 (28) [$M^+ -31$(OMe], 190 (25) [$M^+ -45$ (NOMe)], 173 (22) [$M^+ -62(2 \times$ OMe)], 160 (46), 146 (34), 130 (71), 77 (13). $C_{12}H_{11}NO_4$ (233.2): calcd. C, 61.80; H, 4.75; N, 6.01. Found: C, 61.87; H, 4.69; N, 5.96%.

Ethyl 2-(2-methoxy-3-oxoisoindolin-1-ylidene)acetate (6b). IR (KBr): $\tilde{\nu} = 1728$, 1715 (C=O, cyclicimide & ester), 1632 (C=C, olefin) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): $\delta = 1.44$ (t, $J_{HH} = 5.8$ Hz, 3H, *Me*C.O, ester), 3.94 (s, 3H, *Me*ON), 4.24 (q, $J_{H\text{-}H} = 5.8$ Hz, 2H, H_2C.O, ester), 6.08 (s, 1H, =CH, olefin), 7.76, 7.87 (2d, $J_{H\text{-}H} = 6.8$ Hz, $2 \times 2H$, *H*-Ar) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 170.4$ (C=O, ester), 168.2 (C=O, imide), 146.7 [C(1)], 138.3, 135.2, 133.6, 127.8, 126.8, 125.2 (C-Ar), 85.6 (=*C*H), 62.4 (*Me*ON), 59.6 (O*C*H_2, ester), 15.3 (O*Me*, ester) ppm; MS (EI, 70 eV): *m/z* (%) = 247 (100) [M^+], 203 (36) [$M^+ -45$(OEt)], 189 (15), 173 (20), 160 (51), 146 (42), 130 (51), 77 (18). $C_{13}H_{13}NO_4$ (247.25): calcd. C, 63.15; H, 5.30; N, 5.67. Found: C, 63.23; H, 5.26; N, 5.58%.

2-Methoxy-3-(2-oxoproylidene)isoindolin-1-one (6c). IR (KBr): $\tilde{\nu} = 1723$, 1684 (C=O, cyclicimide & acetyl), 1590 (C=C, olefin) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): $\delta = 2.48$ (s, 3H, *Me*, acetyl), 4.07 (s, 3H, *Me*ON), 6.32 (s, 1H, =C*H*, olefin), 7.78, 7.84 (2d, $J_{H\text{-}H} = 6.8$ Hz, $2 \times 2H$, *H*-Ar) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 173.6$ (C=O, acetyl), 168.6 (C=O, imide), 145.8 [C(3)], 136.8, 133.2, 127.6, 121.2, 127.8 (C-Ar), 89.5 (=*C*H), 62.2 (*Me*ON), 32.6 (*Me*, acetyl) ppm; MS (EI, 70 eV): *m/z* (%) = 217 (62) [M^+], 203 (9) [$M^+ -15$ (CH_3)], 174 (100) [$M^+ -45$ ($NOCH_3$)], 146 (18), 130 (17), 77 (11). $C_{12}H_{11}NO_3$ (217.22): calcd. C, 66.35; H, 5.10; N, 6.45. Found C, 66.42; H, 5.05; N, 6.53%.

2-Methoxy-3-(2-oxo-2-phenylethylidene)isoindolin-1-one (6d). IR (KBr): $\tilde{\nu} = 1730$ (C=O, cyclicimide), 1654 (C=O, benzoyl), 1610 (C=C, olefin) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): $\delta = 4.12$ (s, 3H, *Me*ON), 7.24 (s, 1H, =CH, olefin), 7.64–7.89 (m, 9H, H-Ar & H-Ph) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 193.2$ (C=O, benzoyl), 167.6 (C=O, imide), 144.8 [C(3)], 138.7, 137.2, 138.3, 135.3, 134, 132.5, 128.6, 128.2, 127.9, 125.8, 124.6, 122.6 (*C*-Ar & *C*-Ph), 84.6 (=*C*H), 62.8 (*Me*ON) ppm; MS (EI, 70 eV): *m/z* (%) = 279 (72) [M^+], 249 [$M^+ -31$(OCH_3)], 236 (18) [$M^+ -45$($NOCH_3$)], 106 (100) [C(O]Ph), 77 (52). $C_{17}H_{13}NO_3$ (279.29): calcd. C, 73.11; H, 4.69; N, 5.02. Found: C, 73.19; H, 4.61; N, 5.12%.

2-(2-Methoy-3-oxoisoindolin-1-ylidene)acetonitrile (6e). IR (KBr): $\tilde{\nu} = 2218$ (CN), 1727 (C=O, cyclicimide), 1622 (C=C, olefin) cm^{-1}; ^1H NMR

(500.6 MHz, $CDCl_3$): δ = 4.07 (s, 3H, *Me*ON), 5.63 (s, 1H, =C*H*, olefin), 7.78, 7.84 (2d, $J_{H\text{-}H}$ = 6.8 Hz, 2 × 2H, *H*-Ar) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 167.8 (C=O, imide), 148.2 [C(1)], 137.7, 135.4, 127.2, 126.5, 122.6 (*C*-Ar), 63.2 (=*C*H-CN), 62.7 (*Me*ON) ppm; MS (EI, 70 eV): *m/z* (%) = 200 (90) [M^+], 186 (100) [M^+ −15 (CH_3)], 170 (64), 157 (55), 143 (9), 129 (44), 77 (16). $C_{11}H_8N_2O_2$ (200.2): calcd. C, 66.00; H, 4.03; N, 13.99. Found: C, 66.04; H, 4.11; N, 13.89%.

Reduction of 6a–e. To a mixture of the olefins **6a–e** (2.72 mmol) in EtOH (26 mL) and zinc dust (4.76 g, 73.0 mmol), 6.5 mL of NH_4OAc (1 M) was added slowly into the slurry over a period of 3 min. After 45 min of stirring at rt, a solution of 10 (N) NaOH (0.92 mL) was added to the reaction mixture. The product mixture was filtered through the celite, washed with CH_2Cl_2, and brine was added. The organic phase was separated, and the water phase was extracted with $CHCl_3$. The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was collected and crystallized from the proper solvent to give **7a–e.**

Methyl 2-(2-methoxy-3-oxoisoindol-1-yl)acetate (7a). Pure *E*-isomer, as pale yellow crystals (486 mg, 76%); mp. 142–143 °C (MeCN); IR (KBr): $\tilde{\nu}$ = 1728, 1713 (2C=O, cyclicimide & ester); ^{1}H NMR (500.6 MHz, $CDCl_3$): δ = 3.64 (d, $J_{H\text{-}H}$ = 6.3 Hz, 2H, H_2C-Ar), 3.88 (s, 3H, *Me*O, ester), 4.09 (s, 3H, *Me*ON), 4.54 (t, $J_{H\text{-}H}$ = 6.3 Hz, 1H, C(1)*H*), 7.77, 7.88 (2d, $J_{H\text{-}H}$ = 6.5 Hz, 2 × 2H, *H*-Ar) ppm; δ = ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 168.6 (C=O, imide), 161.7 (C=O, ester), 131.1, 128.4, 126.7, 124.2, 114.8, 94.8 (*C*-Ar), 62.8 (*Me*ON), 52.5 (O*Me*, ester), 42.3 (*C*H_2-Ar), 38.6 [C(1)] ppm; MS (EI, 70 eV): *m/z* (%) = 234 (28) [M^+ −1], 209 (100) [M^+ −28(CO)], 177 (35), 147 (53) [M^+ −90 (CO + 2 × OMe)], 127 (22), 130 (44), 116 (34), 77 (23). $C_{12}H_{13}NO_4$ (235.2): calcd C, 61.27; H, 5.57; N, 5.95: Found C, 61.33; H, 5.51; N, 6.02%.

Ethyl 2-(2-methoxy-3-oxoisoindol-1-yl)acetate (7b). Pure *E*-isomer, as pale yellow crystals (542 mg, 80%); mp 148–150 °C (MeCN); IR (KBr): $\tilde{\nu}$ = 1725, 1714 (2C=O, cyclicimide & ester) cm^{-1}; ^{1}H NMR (500.6 MHz, $CDCl_3$): δ = 1.37 (t, $J_{H\text{-}H}$ = 6.6 Hz, 3H, *Me*CO, ester), 3.76 (d, $J_{H\text{-}H}$ = 8.2 Hz, 2H, H_2C-Ar), 3.88 (s, 3H, *Me*ON), 4.32 (q, J_{HH} = 6.6 Hz, 2H, H_2CO, ester), 4.57 (t, $J_{H\text{-}H}$ = 8.2 Hz, 1H, C(1)*H*), 7.76, 7.87 (2d, $J_{H\text{-}H}$ = 6.5 Hz, 2 × 2H, *H*-Ar) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 167.6, 160.8 (2C=O, cyclicimide & ester), 131.6, 127.8, 126.7, 124.2, 116.8, 94.8 (*C*-Ar), 63.2 (*Me*ON), 62.3 (O*C*H_2), 41.4 (*C*H_2-Ar), 38.3 [C(1)], 14.7 (OC*Me*, ester) ppm; MS (EI, 70 eV): *m/z* (%) = 248 (37) [M^+ −1], 223 (100) [M^+ −28(CO)], 193 (42) [M^+ −59 (CO +OMe], 149 (53), 127 (28), 130 (21), 116 (48), 77 (33). $C_{13}H_{15}NO_4$ (249.26): calcd. C, 62.64; H, 6.04; N, 5.65. Found: C, 62.69; H, 5.98; N, 5.72%.

1-(2-Methoxy-3-oxoisoindol-1-yl)propan-2-one (7c). Pure *E*-isomer, as colorless crystals (464 mg, 78%); mp 158–160 °C ($CHCl_3$); IR (KBr): 158–160 ($CHCl_3$); $\tilde{\nu}$ = 1719, 1682 (2C=O, cyclicimide & acetyl) cm^{-1}; ^{1}H NMR (500.6 MHz, $CDCl_3$): δ = 2.48 (s, 3H, *Me*.acetyl), 3.78 (d, $J_{H\text{-}H}$ = 7.2 Hz, 2H, H_2C-Ar), 4.07 (s, 3H, *Me*ON), 4.72 [t, $J_{H\text{-}H}$ = 7.2 Hz, 1H, C(1)*H*], 7.78, 7.84 (2d, $J_{H\text{-}H}$ = 6.8 Hz, 2 × 2H, H-Ar) ppm; ^{13}C NMR (125.9 MHz, $CDCl_3$): δ = 205.7 (C=O, acetyl),168.4 (*C*=O, imide), 129.6, 128.4, 126.7, 124.2, 118.8, 94.2 (*C*-Ar),

62.8 (*Me*ON), 33.6 (*C*H_2-Ar), 40.6 [*C*(1)], 22.6 (*Me*, acetyl) ppm; MS (EI, 70 eV): *m/z* (%) = 218 (47) [$M^+ -1$], 193 (100) [$M^+ -28$(CO)], 163 (18), 148 (65), 127 (18), 130 (44), 116 (46), 77 (37). $C_{12}H_{13}NO_3$ (219.24): calcd. C, 65.74; H, 5.98; N, 6.39. Found: C, 65.80; H, 6.03; N, 6.32%.

2-(2-Methoxy-3-oxoisoindol-1-yl)-1-phenylethanone (7d). Pure *E*-isomer, as colorless crystals (610 mg, 80%); mp 144–145 °C; (MeCN); IR (KBr): $\tilde{\nu}$ = 1732, 1656 (2C=O, cyclicimide & benzoyl) cm^{-1}; ^{1}H NMR (500.6 MHz, $CDCl_3$): δ = 3.75 (d, $J_{H\text{-}H}$ = 6.8 Hz, 2H, H_2C-Ar), 4.16 (s, 3H, *Me*ON), 4.66 (t, $J_{H\text{-}H}$ = 6.8 Hz, 1H, C(1)*H*), 7.64–7.89 (m, 9H, *H*-Ar & *H*-Ph) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 196.3 (C=O, benzoyl), 165.5 (C=O, imide), 133.8, 131.2, 130.6, 129.2, 128.2, 127.9, 123.8, 1156, 91.6 (*C*-Ar & *C*-Ph), 63.2 (*Me*ON), 36.6 [*C*(1)], 28.6 (*C*H_2-Ar) ppm; MS (EI, 70 eV): *m/z* (%) = 280 (22) [$M^+ -1$], 255 (56) [$M^+ -28$(CO)], 210 (42) [$M^+ -73$(CO +$NOCH_3$)], 105 (100) (C(O)Ph), 77 (55). $C_{11}H_8N_2O_2$ (200.2): $C_{17}H_{15}NO_3$ (281.31): calcd. C, 72.58; H, 5.37; N, 4.98. Found: C, 72.64; H, 5.32; N, 5.03%.

2-(2-Methoxy-3-oxoisoindol-1-yl)acetonitrile (7e). Pure *E*-isomer, as pale yellow crystals (mg, 76%); mp (395 mg, 72%); mp 194–196 °C; (EtOH); IR (KBr): $\tilde{\nu}$ = 2220 (CN), 1721 (C=O, cyclicimide) cm^{-1}; ^{1}H NMR (500.6 MHz, $CDCl_3$): δ = 3.85 (d, $J_{H\text{-}H}$ = 7.8 Hz, 2H, H_2C-Ar), 4.17 (s, 3H, *Me*ON), 4.55 [t, $J_{H\text{-}H}$ = 7.8 Hz, Hz, 1H], C(1)*H*), 7.78, 7.87 (2d, $J_{H\text{-}H}$ = 6.5 Hz, 2 × 2H, *H*-Ar) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 169, 164.3 (2C=O, cyclicimide & ester), 130.6, 129.4, 126.7, 125.2, 122.4, 96.3 (*C*-Ar), 114.6 (CN), 63.5 (*Me*ON), 38.6 [*C*(1)] ppm; MS (EI, 70 eV): *m/z* (%) = 201 (60) [$M^+ -1$], 174 (66) [$M^+ -28$ (CO)], 148 (100), 118 (55), 111 (9), 77 (16). $C_{11}H_{10}N_2O_2$ (202.21): calcd. C, 65.34; H, 4.98; N, 13.85. Found: C, 65.44; H, 4.94; N, 13.91%.

Reaction of **1** with two molar amounts of **4a–e** under the previous experimental conditions yielded only the same products **6a–e**.

Under microwave condition, general procedure B. Compound **1** (2.8 mmol), 0.5 g was added to a solution mixture of 8 mL dry dimethylsulfoxide (DMSO) and ≈ 2.85 mmol of **4a, 4b, 4c, 4d** or **4e**) in a Pyrex glass beaker. Microwave irradiation (MW domestic type oven 1000 W with a frequency 2450 of MHz, National Jp) was applied for 8–10 min (each pulse of 2 min). After the completion of the reaction and the usual workup, the resulting residue was chromatographed on silica gel (*n*-hexane/$CHCl_3$) to give the respective olefin as the sole reaction products **6a** (84), **6b** (85), **6c** (82), **6d** (78), or **6e** (87%).

Reaction of *N*-Anilinophthalimide (2) with Wittig Reagents 4a,b: Synthesis of 8a,b

Under thermal conditions. A mixture of 6.4 mmol of **4a** or **4b** and 1.5 g (6.3 mmol) of **2** in 40 mL of dry toluene was heated under reflux for ≅20 h (TLC). After removal of the solvent, the residue was chromatographed on silica gel using *n*-hexane/$CHCl_3$ as eluents to give the respective product **8a** or **8b** (see Table 1). Triphenylphosphine oxide (TPPO) was also isolated (6:4 v/v) and identified from both reactions.

Methyl 2-(3-oxo-2-(phenylamino)isoindolin-1-ylidene)acetate (8a). IR (KBr): $\tilde{\nu}$ = 1732, 1710 (C=O, cyclicimide & ester), 1618 (C=C, olefin) cm^{-1}; ^{1}H

NMR (500.6 MHz, $CDCl_3$): δ = 3.78 (s, 3H, *Me*O, ester), 6.18 (s, 1H, =C*H*, olefin), 7.36–7.88 (m, 9H, *H*-Ar), 8.86 (s, 1H, *H*N, exch with D_2O) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.2 (C=O, imide), 169.6 (C=O, ester), 144.8 [*C*(1)], 139.7, 136.5, 133.2, 130.2, 129.6, 126.1, 125.8, 125.2, 124.7, 122.6, 114.2 (*C*-Ar & *C*-Ph), 84.6 (Ar=*C*H), 52.3 (O*Me*, ester) ppm; MS (EI, 70 eV): *m/z* (%) = 294 (100) [M^+], 280 (16) [M^+ −15 (Me)], 264 (100) [M^+ −31(OMe)], 203 (22) [M^+ − 92 (NHPh], 179 (14), 129 (14), 92 (20), 77 (46). $C_{17}H_{14}N_2O_3$ (294.3): calcd. C, 69.38; H, 4.79; N, 9.52. Found: C, 69.51; H, 4.77; N, 9.43%.

Ethyl 2-(3-oxo-2-(phenylamino)isoindolin-1-ylidene)acetate (8b). IR (KBr): $\tilde{\nu}$ = 1732, 1718 (C=O, cyclicimide & ester), 1614 (C=C, olefin) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): δ = 1.34 (t, J_{HH} = 6.8 Hz, 3H, *Me*C.O, ester), 4.28 (q, $J_{H\text{-}H}$ = 6.8 Hz, 2H, H_2CO, ester), 6.34 (s, 1H, =CH, olefin), 7.45–7.87 (m, 9H, *H*-Ar), 9.26 (s, 1H, *H*N, exch with D_2O) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 173.2, 169.4 (2C=O, imide, ester), 144.7 [*C*(1)], 138.1, 135.6, 134.1, 129.8, 129.6, 126.3, 125.2, 124.7, 124.1, 121.6, 115.7 (*C*-Ar & *C*-Ph), 85.6 (Ar=*C*H), 62.4 (CH_2O) ppm; MS (EI, 70 eV): *m/z* (%) = 308 (100) [M^+], 264 (72) [M^+ −45(OEt))], 217 (18) [M^+ −92 (NHPh], 179 (14), 129 (20), 92 (13), 77 (16). $C_{18}H_{16}N_2O_3$ (308.34): calcd. C, 70.12; H, 5.23; N, 9.09. Found: C, 70.17; H, 5.31; N, 8.98%.

Compounds **8a** and **8b** in 82 and 85% yields were obtained by carrying out these two reactions under the microwave conditions. On the other hand, no reaction was observed when **2** was allowed to react, under the same conditions, with **4c, 4d**, or **4e**.

Preparation of 9a, 9b. These compounds were prepared from **8a, b** by applying the same protocol adopted for the preparation of **7a–e** from **6a–e**.

Methyl 2-(2-(phenylamino)-3-oxoisoindol-1-yl)acetate (9a). Pure *E*-isomer, as pale yellow crystals (660 mg, 82%); mp 231–233 °C ($CHCl_3$); IR (KBr): $\tilde{\nu}$ = 1722, 1715 (2C=O, cyclicimide & ester) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): δ = 3.82 (d, $J_{H\text{-}H}$ = 6.8 Hz, 2H, H_2C-Ar), 3.85 (s, 3H, *Me*O, ester), 4.72 (t, $J_{H\text{-}H}$ = 6.8 Hz, 1H, C(1)*H*), 7.36–7.88 (m, 9H, *H*-Ar), 9.46 (s, 2 × 1H, *H*N, exch with D_2O) ppm; MS (EI, 70 eV): *m/z* (%) = 295 (38) [M^+ −1]. $-C_{18}H_{18}N_2O_3$ (310.35): calcd. C, 69.66; H, 5.85; N, 9.03. Found: C, 70.01; H, 5.91; N, 9.09.

Ethyl 2-(2-(phenylamino)-3-oxoisoindol-1-yl)acetate (9b). Pure *E*-isomer, as pale yellow crystals (715 mg, 85%); mp 189–190 °C ($CHCl_3$); IR (KBr): $\tilde{\nu}$ = 1728, 1713 (2C=O, cyclicimide & ester) cm^{-1}; ^1H NMR (500.6 MHz, $CDCl_3$): δ = 1.23 (t, $J_{H\text{-}H}$ = 7 Hz, 3H, *Me*CO, ester), 3.87 (d, $J_{H\text{-}H}$ = 7.6 Hz, 2H, H_2C-Ar), 4.22 (q, $J_{H\text{-}H}$ = 7 Hz, 2H, H_2CO, ester), 4.72 [t, $J_{H\text{-}H}$ = 7.6 Hz, 1H, C(1]*H*), 7.45–7.87 (m, 9H, *H*-Ar), 9.26 (s, 1H, *H*N, exch. D_2O) ppm; MS (EI, 70 eV): *m/z* (%) = 309 (33) [M^+ −1], -$C_{17}H_{16}N_2O_3$ (296.3): calcd. C, 68.91; H, 5.44; N, 9.45. Found: C, 69.01; H, 5.37; N, 9.51%.

Anti-Inflammatory Activity Experiments In Vivo: Carrageenin-Induced Edema

All compounds tested were dispersed in sterilized saline with a concentration of 0.11 mmol/kg, stabilized by 0.05% Tween-80 (vehicle solution) and administered intraperitoneally. Fisher 344 male and female rats (pregnant excluded) weighing

180–220 g were used. The animals were divided into 12 groups of 6 animals each and housed under standard conditions. Indomethacin, **A** (0.11 mmol/kg body weight) was administered as a standard drug.

Acute anti-inflammatory activity[20] (Table 1) was measured after 3.5 h by reduction of rat paw carrageenin edema, induced by injection of 0.1 mL carrageenin 2% (K100, commercially available) in sterilized saline, intradermally into the right foot pad. The examined compounds (previously prepared in the vehicle solution) were administered simultaneously to the animals. Paw volumes were measured volumetrically after 3.5 h with plethysmometer 7150 (UGO BASILE, Italy) and compared with the initial hind paw volume of each rat for determining the edema volume. Data were collected, checked, revised, and analyzed. Quantitative variables from normal distribution were expressed as means ±SE. The significant difference between groups was tested by using one-way (ANOVA) followed by least significiant difference (LSD) test (P).

The anti-inflammatory activity was expressed as percentage inhibition of edema volume in treated animals in comparison with the control group, and the data are collected in Table 2.

$$\%\ \text{Inhibition of edema} = \frac{(V_c - V_t)}{V_c} \times 100$$

where V_c and V_t are the volumes of edema for the control and drug-treated animal groups, respectively, while potency of the tested compounds was calculated regarding indomethacin, reference standard, in the treated group according to the following equation:

$$\text{Potency} = \frac{\%\ \text{Edema inhibition of tested compound treated group}}{\%\ \text{Edema inhibition of Indomethacin treated group}}$$

Toxicity of the Evaluated Phosphorus Heterocycles

The LD_{50} determination of the most promising synthesized anti-inflammatory active agents (**7Aa,b**, **9Aa**, and **9Ab**) was determined the standard known LD_{50} method in mice.[21] Albino mice weighing 20–25 g were divided into 6 groups of 8 mice each. Administrations of the tested compounds (**7Aa,b**, **9Aa**, and **9Ab**) dissolved in the same vehicle solution in 500, 750, and 1000 mg/kg (body weight) were given intraperitoneally. The control groups were given in buffer solution only. The toxic symptoms, mortality rates, and postmortem findings in each group were recorded 24 h postadministration.

LD_{50} of the tested compounds were calculated according to the following formula:

$$LD_{50} = D_m - \Sigma(z \times d)/n$$

where D_m is the largest dose that kills all animals, z is mean of dead animals between two successive groups, d is the constant factor between two successive doses, n is the number of animals in each group, and Σ is the sum of $(z \times d)$.

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