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One-pot synthesis of functionalized furamide derivatives via a three-component reaction between an amine, diketene and dibenzoylacetylene in the presence of triphenylphosphine

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Abstract—An effective route to functionalized furamide derivatives is described. This involves reaction of *N*-alkyl-3-oxobutanamides, derived from the addition of amines to the diketene, and dibenzoylacetylene in the presence of triphenylphosphoine. The reactive 1:1 intermediate obtained from the addition of triphenylphosphine to dibenzoylacetylene was trapped by OH-acids such as *N*-alkyl-3-oxobutanamide to produce functionalized furamide derivatives.

1. Introduction

Recently, multicomponent condensation reactions have become one of the most powerful methods for the synthesis of small molecule libraries, due to the fact that products are formed in a single step by simultaneous reactions of several reagents and the molecular diversity required for such combinatorial libraries can be achieved by simply varying each component.[1]

Substituted furans play an important role in organic chemistry, not only as key structural units in many natural products and important pharmaceuticals[2,28] but also as useful building blocks in synthetic chemistry.[3] While many synthetic routes for furan synthesis exist, convergent annulation strategies without transition-metal catalysis are uncommon.[4,5]

Fungal infections are associated with rates of attributable morbidity and mortality. Limited therapeutic options for treating these infections, as well as concerns over selection of non-*Candida* species with reduced susceptibilities to the triazole agents, have warranted surveillance for potential resistance development and demonstrated the need for expansion of available antifungal regimens.[6–9]

Furan derivatives, obtained from both synthetic and natural sources, have been attracting much interest due to the wide range of pharmaceutical applications.[10–12] Many of the naturally occurring furans have shown interesting biological activities, such as cytotoxic and antitumor properties,[12,13] as well as antispasmodic,[14] antimicrobial,[15,16] and several other potentially useful activities.[17] A series of synthetic nitrofuranyl amides showed good in vitro inhibitory activity against *Mycobacterium tuberculosis*,[18,19] especially 5-nitro-furan-2-carboxylic acid *N*-[4-(4-benzylpiperazin-1-yl)-benzyl]-5-nitrofuran-2-carboxamide[18] and 2-methyl-*N*-phenylfuran-3-carboxamide, commercially known as Fenfuran,[20] which is used as fungicidal seed dressing for the control of bunts and smuts. In addition, furans are also present in commercially important products such as agrochemical bioregulators, dyes and photosensitizers, essential oils, cosmetics, and flavoring and fragrance compounds.[21–23]

Although a variety of furan syntheses are known, the development of new and convenient strategies to synthesize them is of considerable interest.[24] Furans can be, in principle, synthesized by either cyclization of acyclic precursors[25–27] or by derivatization of the furan ring.[28] Introduction of substituents at the 2- or 5-position of furan is relatively easy to carry out by electrophilic aromatic substitution,[23] whereas a different strategy is necessary to obtain 3- or 4-substituted furans.[29] Many methodologies to functionalize position 3 or 4 of furans have been reported, however, most of them involve multi-step synthesis,[30–32] modification of butyrolactone derivatives,[33] or the use of expensive reagents.[34] In addition, there is a paucity of methods to make furans containing carboxamide groups at the 3- or 4-position in the literature.[35] For these reasons, there is a clear demand for the development of a modular and simple reaction to access strategically substituted furans.

Keywords: Amine; Diketene; Dibenzoylacetylene; Triphenylphosphine; Furamide; Multicomponent reaction.
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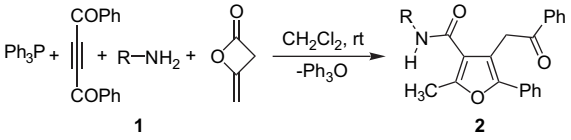
Although the trapping of the 1:1 intermediate formed between triphenylphosphine and dibenzoylacetylene with O–H, N–H, and C–H acids has been studied in detail by our research group,[35,36] trapping of the initially formed 1:1 intermediate with *N*-alkyl-3-oxobutanamide has not been reported.

We wish to report a simple one-pot three-component reaction between an amine, diketene and dibenzoylacetylene in the presence of triphenylphosphine leading to yield N^3-(alkyl)-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide derivatives **2**.

2. Results and discussion

The reaction of *N*-alkyl-3-oxobutanamide **3**, which was derived from the addition of a primary amine **2** to diketene, with dibenzoylacetylene in the presence of triphenylphosphine proceeds in dichloromethane at ambient temperature, to produce N^3-(alkyl)-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide derivatives **2** in 80–90% yields (Scheme 1).



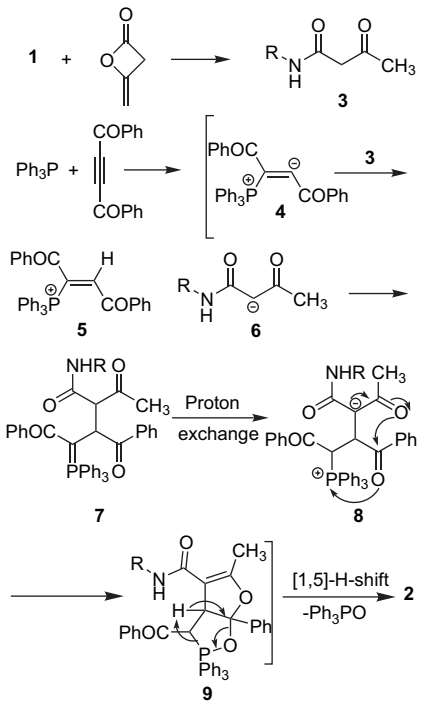
1,2	R	%Yield of **2**
a	*s*-Bu	90
b	*i*-Bu	87
c	*t*-Bu	80
d	allyl	80
e	$C_6H_5CH_2$	90
f	*o*-$ClC_6H_4CH_2$	90
g	2-Ethylhexyl	85

Scheme 1.

The structures of compounds **2a–g** was deduced from their spectral data.

Although the mechanism of the reaction between triphenylphosphine and dibenzoylacetylene in the presence of *N*-alkyl-3-oxobutanamide **3**, which derived from the addition of an amine to diketene, has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2.

Based on the well-established chemistry of trivalent phosphorus nucleophiles,[37–43] it is reasonable to assume that **2** results from initial addition of triphenylphosphine to dibenzoylacetylene and subsequent protonation of the 1:1 adduct by the *N*-alkyl-3-oxobutanamide as OH-acid. Then, the positively charged ion might be attacked by the conjugate base of the OH-acid to form phosphorane **7**, which in turn is converted to betaine **8**. Cyclization of the betaine **8** and subsequent loss of triphenylphosphine oxide leads to compound **2** (see Scheme 2).



Scheme 2.

3. Conclusion

In conclusion, the present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multi-step approaches.

4. Experimental

Amines and diketene were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Dibenzoylacetylene was prepared according to the literature procedure.[44,45] Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 20 eV. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh.

4.1. General procedure for preparation of compound 2a–g: Preparation of 2a

A magnetically stirred solution of 0.073 g of *sec*-butylamine (1 mmol) and 0.084 g of diketene (1 mmol) in 5 mL of dry CH_2Cl_2 for 5 h and then 0.26 g of triphenylphosphine (1 mmol), and a solution of 0.23 g of dibenzoylacetylene (1 mmol) in 3 mL of dry CH_2Cl_2 was added dropwise at room temperature over 10 min. The reaction mixture was

then allowed to stir for 2 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel (Merck 230–240 mesh) column chromatography using a hexane–ethyl acetate mixture 4:1 as eluant. The furans were then recrystallized from ethanol.

4.1.1. N^3-(*sec*-Butyl)-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide (2a). White powder (0.34 g, 90%), mp 150–152 °C (dec). [Found: C, 77.00; H, 6.50; N, 3.80; $C_{24}H_{25}NO_3$ requires C, 76.78; H, 6.71; N, 3.73%.] R_f (25% EtOAc/hexane) 0.44; ν_{max} (KBr) 3250 (NH), 1675 (C=O), 1620 (CONH), 1531 and 1433 cm^{-1} (Ar). δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.4 Hz, CH_3CH_2), 1.11 (3H, d, *J* 6.6 Hz, CH_3CH), 1.45 (2H, m, CH_2CH), 2.55 (3H, s, CH_3), 3.98 (1H, m, CH_2CH), 4.42 (2H, s, CH_2), 6.29 (1H, d, *J* 7.5 Hz, NH), 7.28 (1H, t, *J* 7.2 Hz, CH of Ar), 7.33 (2H, t, *J* 7.5 Hz, 2CH of Ar), 7.38 (2H, d, *J* 7.0 Hz, 2CH of Ar), 7.51 (2H, t, *J* 7.6 Hz, 2CH of Ar), 7.63 (1H, t, *J* 7.4 Hz, CH of Ar), 8.06 (2H, d, *J* 7.3 Hz, 2CH of Ar). δ_C (125 MHz, $CDCl_3$) 10.31 (CH_3CH_2), 13.33 (CH_3), 20.39 (CH_3CH), 29.63 (CH_2CH), 35.24 (CH_2CO), 46.52 (CH_2CH), 112.70 (C_3 of furan), 120.87 (C_4 of furan), 126.55 (2CH of Ar), 127.89 (CH of Ar), 128.47 (2CH of Ar), 128.66 (2CH of Ar), 128.83 (2CH of Ar), 130.38 (C_{ipso}–furyl), 133.73 (CH of Ar), 136.41 (C_{ipso}–$COCH_2$), 149.66 (C_5 of furan), 152.57 (C_2 of furan), 164.10 (CONH), 199.28 (COPh). MS, *m*/*z* (%): 375 (M^+, 9), 302 (100), 214 (6), 199 (18), 105 (44), 77 (28), 43 (7).

4.1.2. N^3-(*iso*-Butyl)-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide (2b). White powder (0.32 g, 87%), mp 130–132 °C (dec). [Found: C, 77.00; H, 6.50; N, 3.80; $C_{24}H_{25}NO_3$ requires C, 76.78; H, 6.71; N, 3.73%.] R_f (25% EtOAc/hexane) 0.46; ν_{max} (KBr) 3285 (NH), 1675 (C=O), 1635 (CONH), 1610 (Ar), 1437 cm^{-1} (Ar). δ_H (500 MHz, $CDCl_3$) 0.89 (6H, d, *J* 6.7, $2CH_3$ of isobutyl), 1.75 (1H, m, CH of isobutyl), 2.57 (3H, s, CH_3), 3.17 (2H, t, *J* 6.3 Hz, CH_2 of isobutyl), 4.44 (2H, s, CH_2), 6.57 (1H, t, *J* 6.3 Hz, NH), 7.28 (1H, t, *J* 7.1 Hz, CH of Ar), 7.31 (2H, t, *J* 7.0 Hz, 2CH of Ar), 7.37 (2H, d, *J* 7.4 Hz, 2CH of Ar), 7.50 (2H, t, *J* 7.8 Hz, 2CH of Ar), 7.63 (1H, t, *J* 7.4 Hz, CH of Ar), 8.06 (2H, d, *J* 7.4 Hz, 2CH of Ar). δ_C (125 MHz, $CDCl_3$) 13.45 (CH_3), 20.16 ($2CH_3$ of isobutyl), 28.49 (CH of isobutyl), 35.18 (CH_2), 46.97 (CH_2 of isobutyl), 112.77 (C_3 of furan), 120.70 (C_4 of furan), 126.54 (2CH of Ar), 127.91 (CH of Ar), 128.52 (2CH of Ar), 128.66 (2CH of Ar), 128.83 (2CH of Ar), 130.35 (C_{ipso}–furyl), 133.75 (CH of Ar), 136.35 (C_{ipso}–CO), 149.63 (C_5 of furan), 152.79 (C_2 of furan), 164.80 (CONH), 199.33 (C=O). MS, *m*/*z* (%): 375 (M^+, 9), 302 (100), 199 (24), 105 (52), 77 (36), 43 (14).

4.1.3. N^3-(*tert*-Butyl)-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide (2c). White powder (0.30 g, 80%), mp 146–148 °C (dec). [Found: C, 77.00; H, 6.50; N, 3.80; $C_{24}H_{25}NO_3$ requires C, 76.78; H, 6.71; N, 3.73%.] R_f (25% EtOAc/hexane) 0.53; ν_{max} (KBr) 3280 (NH), 1672 (C=O), 1636 (CONH), 1584 and 1516 cm^{-1} (Ar). δ_H (500 MHz, $CDCl_3$) 1.33 (9H, s, CMe_3), 2.54 (3H, s, CH_3), 4.41 (2H, s, CH_2), 6.28 (1H, s, NH), 7.28 (1H, t, *J* 8.8 Hz, CH of Ar), 7.33 (2H, t, *J* 7.56 Hz, 2CH of Ar), 7.37 (2H, d, *J* 8.0 Hz, 2CH of Ar), 7.51 (2H, t, *J* 7.9 Hz, 2CH of Ar), 7.64 (1H, t, *J* 7.40 Hz, CH of Ar), 8.06 (2H, d, *J* 7.2 Hz, 2CH of Ar). δ_C (125 MHz, $CDCl_3$) 13.23 (CH_3), 28.84 (CMe_3), 35.28 (CH_2), 51.32 (CMe_3), 112.64 (C_3 of furan), 121.70 (C_4 of furan), 126.51 (2CH of Ar), 127.84 (CH of Ar), 128.45 (2CH of Ar), 128.66 (2CH of Ar), 128.85 (2CH of Ar), 130.44 (C_{ipso}–furyl), 133.72 (CH of Ar), 136.42 (C_{ipso}–CO), 149.46 (C_5 of furan), 152.45 (C_2 of furan), 164.18 (CONH), 199.19 (CO). MS, *m*/*z* (%): 375 (M^+, 5), 302 (92), 214 (24), 198 (17), 141 (9), 105 (100), 77 (78), 57 (13), 43 (16).

4.1.4. N^3-Allyl-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide (2d). White powder (0.29 g, 80%), mp 113–115 °C (dec). [Found: C, 78.00; H, 6.00; N, 3.80; $C_{23}H_{21}NO_3$ requires C, 76.86; H, 5.89; N, 3.90%.] R_f (25% EtOAc/hexane) 0.38; ν_{max} (KBr) 3300 (NH), 1679 (C=O), 1640 (CONH), 1590 and 1514 (Ar). δ_H (500 MHz, $CDCl_3$) 2.57 (3H, s, CH_3), 3.96 (2H, t, *J* 5.6 Hz, CH_2N), 4.45 (2H, s, CH_2), 5.09 (1H, dd, *J* 10.3 Hz, *J* 1.0 Hz, CH=CH_2), 5.19 (1H, dd, *J* 17.2 Hz, *J* 1.3 Hz, CH=CH_2), 5.83 (1H, m, CH=CH_2), 6.57 (1H, broad, NH), 7.28 (1H, t, *J* 7.1 Hz, CH of Ar), 7.33 (2H, t, *J* 7.0 Hz, 2CH of Ar), 7.39 (2H, d, *J* 7.1 Hz, 2CH of Ar), 7.50 (2H, t, *J* 7.8 Hz, 2CH of Ar), 7.62 (1H, t, *J* 7.4 Hz, CH of Ar), 8.05 (2H, d, *J* 7.4 Hz, 2CH of Ar). δ_C (125 MHz, $CDCl_3$) 13.52 (CH_3), 35.09 (CH_2CO), 41.95 (CH_2NH), 112.97 (C_3 of furan), 116.36 (CH=CH_2), 120.27 (C_4 of furan), 126.57 (2CH of Ar), 127.95 (CH of Ar), 128.53 (2CH of Ar), 128.67 (2CH of Ar), 128.80 (2CH of Ar), 130.31 (C_{ipso}–furyl), 133.69 (CH of Ar), 134.11 (CH=CH_2), 136.43 (C_{ipso}–CO), 149.71 (C_5 of furan), 152.91 (C_2 of furan), 164.59 (CONH), 199.20 (COPh). MS, *m*/*z* (%): 359 (M^+, 3), 302 (45), 199 (14), 171 (18), 105 (94), 77 (100), 51 (18), 43 (22).

4.1.5. N^3-Benzyl-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide (2e). White powder (0.36 g, 90%), mp 167–169 °C (dec). [Found: C, 79.00; H, 6.10; N, 3.50; $C_{27}H_{23}NO_3$ requires C, 79.20; H, 5.66; N, 3.42%.] R_f (25% EtOAc/hexane) 0.34; ν_{max} (KBr) 3250 (NH), 1675 (C=O), 1620 (CONH), 1531 and 1433 cm^{-1} (Ar). δ_H (500 MHz, $CDCl_3$) 2.56 (3H, s, CH_3), 4.42 (2H, s, CH_2), 4.52 (2H, d, *J* 5.6 Hz, $PhCH_2$), 6.81 (1H, broad, NH), 7.18–7.27 (5CH of Ar), 7.29 (1H, d, *J* 7.0 Hz, CH of Ar), 7.33 (2H, t, *J* 7.6 Hz, 2CH of Ar), 7.39 (2H, d, *J* 7.3 Hz, 2CH of Ar), 7.48 (2H, t, *J* 7.6 Hz, 2CH of Ar), 7.62 (1H, t, *J* 7.3 Hz, CH of Ar), 7.98 (2H, d, *J* 7.6 Hz, 2CH of Ar). δ_C (125 MHz, $CDCl_3$) 13.50 (CH_3), 35.27 (CH_2), 43.63 (CH_2Ph), 112.93 (C_3 of furan), 120.26 (C_4 of furan), 126.56 (2CH of Ar), 127.30 (CH of Ar), 127.67 (2CH of Ar), 127.96 (CH of Ar), 128.50 (2CH of Ar), 128.61 (2CH of Ar), 128.69 (2CH of Ar), 128.75 (2CH of Ar), 130.30 (C_{ipso}–furyl), 133.66 (CH of Ar), 136.33 (C_{ipso}–$COCH_2$), 138.33 (C_{ipso}–CH_2NH), 149.75 (C_5 of furan), 153.01 (C_2 of furan), 164.62 (CONH), 199.17 (COPh). MS, *m*/*z* (%): 409 (M^+, 8), 302 (100), 275 (6), 199 (21), 171 (7), 129 (6), 105 (91), 91 (58), 77 (65), 43 (13).

4.1.6. N^3-(2-Chlorobenzyl)-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide (2f). White powder (0.40 g, 90%), mp 130–132 °C (dec). [Found: C, 76.00; H, 5.10; N, 3.50; $C_{27}H_{22}NO_3$ requires C, 73.05; H, 4.99; N, 3.16%.]; R_f (25% EtOAc/hexane) 0.45; ν_{max} (KBr) 3290 (NH), 1672

(C═O), 1636 (CONH), 1513 (Ar), 690 cm^{-1} (C–Cl). δ_H (500 MHz, $CDCl_3$) 2.57 (3H, s, CH_3), 4.43 (2H, s, CH_2CO), 4.60 (2H, d, *J* 5.8 Hz, PhCH_2), 6.95 (1H, t, *J* 5.0 Hz, NH), 7.13 (1H, t, *J* 7.5 Hz, CH of Ar), 7.18 (1H, d, *J* 7.2 Hz, CH of Ar), 7.23 (1H, d, *J* 7.2 Hz, CH of Ar), 7.28 (1H, d, *J* 8.3 Hz, CH of Ar), 7.33 (2H, t, *J* 7.2 Hz, 2CH of Ar), 7.33–7.39 (3CH of Ar), 7.48 (2H, t, *J* 7.5 Hz, 2CH of Ar), 7.62 (1H, t, *J* 7.6 Hz, CH of Ar), 7.98 (2H, d, *J* 8.1 Hz, 2CH of Ar). δ_C (125 MHz, $CDCl_3$) 13.50 (*C*H_3), 35.21 (*C*H_2CO), 41.68 (*C*H_2N), 112.90 (C_3 of furan), 120.12 (C_4 of furan), 126.56 (2CH of Ar), 127.00 (CH of Ar), 127.96 (CH of Ar), 128.51 (2CH of Ar), 128.69 (2CH of Ar), 128.74 (2CH of Ar), 128.80 (CH of Ar), 129.44 (CH of Ar), 130.28 (C_{ipso}–furyl), 130.33 (CH of Ar), 133.58 (C_{ipso}–Cl), 133.67 (CH of Ar), 135.72 (C_{ipso}–CH_2N), 136.28 (C_{ipso}–CO), 149.73 (C_5 of furan), 153.36 (C_2 of furan), 164.59 (*C*ONH), 199.20 (*C*OPh). MS, *m*/*z* (%): 444 (M^+, 2), 302 (50), 199 (15), 171 (10), 125 (33), 105 (100), 77 (98), 51 (15), 43 (14).

4.1.7. N^3-(2-Ethylhexyl)-2-methyl-4-(2-oxo-2-phenylethyl)-5-phenyl-3-furamide (2g). White powder (0.37 g, 85%), mp 120–122 °C (dec). [Found: C, 78.00; H, 6.50; N, 3.50; $C_{28}H_{33}NO_3$ requires C, 77.93; H, 7.71; N, 3.25%.] R_f (25% EtOAc/hexane) 0.65; ν_{max} (KBr) 3305 (NH), 1679 (C═O), 1643 (CONH), 1521 cm^{-1} (Ar). δ_H (500 MHz, $CDCl_3$) 0.82 (3H, t, *J* 7.4 Hz, CH_3), 0.83 (3H, t, *J* 6.5 Hz, CH_3), 1.21–1.30 (6H, m, 3CH_2), 1.41 (1H, m, C*H*), 2.57 (3H, s, CH_3), 3.29 (2H, m, CH_2N), 4.43 (2H, s, CH_2CO), 6.46 (1H, broad, NH), 7.28 (1H, t, *J* 8.0 Hz, CH of Ar), 7.31 (2H, t, *J* 7.6 Hz, 2CH of Ar), 7.37 (2H, d, *J* 7.1 Hz, 2CH of Ar), 7.51 (2H, t, *J* 7.9 Hz, 2CH of Ar), 7.64 (1H, t, *J* 7.5 Hz, CH of Ar), 8.06 (2H, d, *J* 7.4 Hz, 2CH of Ar). δ_C (125 MHz, $CDCl_3$) 10.86 (*C*H_3), 13.41 (*C*H_3), 14.03 (*C*H_3), 22.97 (*C*H_2CH_3), 24.34 (*C*H_2CH_3), 28.89 (*C*H_2CH), 31.25 (*C*H_2CH), 35.29 (*C*H_2CO), 39.39 (*C*H), 42.17 (*C*H_2N), 112.62 (C_3 of furan), 120.81 (C_4 of furan), 126.51 (2CH of Ar), 127.89 (CH of Ar), 128.55 (2CH of Ar), 128.66 (2CH of Ar), 128.83 (2CH of Ar), 130.36 (C_{ipso}–furyl), 133.80 (CH of Ar), 136.25 (C_{ipso}–CO), 149.58 (C_5 of furan), 152.95 (C_2 of furan), 164.88 (*C*ONH), 199.36 (*C*O). MS, *m*/*z* (%): 431 (M^+, 6), 302 (100), 199 (14), 171 (4), 105 (28), 77 (12), 43 (11).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.021.

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