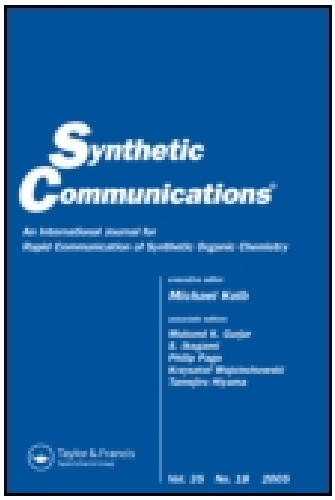

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CYCLIC HYDROXAMIC ACIDS AS OXYGENATING AGENTS – CONVERSION OF IMINES TO ANILIDES

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ABSTRACT

Cyclic hydroxamic acid mediated functional group modification of an imine to anilide is reported.

During our search for novel heterocyclics of medicinal importance, we discovered that cyclic hydroxamic acids can mediate the functional group modification of an imine to amide. The procedure involves heating an equimolar mixture of arylideneaniline (**1a–f**) and 2-phenyl-3-hydroxyquinazolin-4(3*H*)-one (**2**) under microwave irradiation for 6–8 min, and chromatographing the melt over neutral alumina (~150 mesh) using petroleum ether-benzene (6 : 4) as eluent. The corresponding anilide (**3a–f**) was isolated in 48–67% yield. 2-Phenyl-quinazolin-4(3*H*)-one (**4**) was a co-product.

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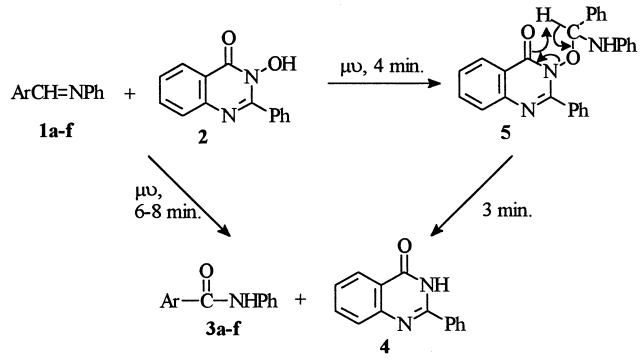
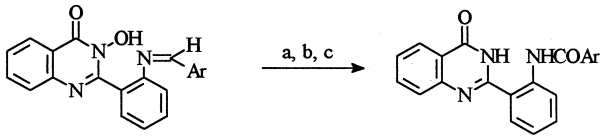
A third product characterised as 3-(α-phenylamino)-benzyloxy-2-phenylquinazolin-4 (3*H*)-one[1] (**5**, mp 182°C) was also isolated in the reaction of **1a** and **2** (4 min). When **5** was independently heated under microwave irradiation for 3 min, it readily underwent retro-ene reaction yielding **4** and benzanilide. The EI mass spectrum (70 eV) of **5** also showed an intense ion peak at *m*/*z* 222 (92%). Isolation of **5** in the reaction of **1a** and **2**, and its subsequent conversion to **3a** and **4**, proved its intermediacy in the formation of **3a** from **1a**.



1 & 3	a	b	c	d	e	f
Ar	C_6H_5	4-$H_3CC_6H_4$	4-$H_3COC_6H_4$	4-ClC_6H_4	4-$NO_2C_6H_4$	3,4-$Cl_2C_6H_3$

The imine–amide conversion described above also occurred intramolecularly. For example, the Schiff's base, 2-[2-(4-methoxybenzylideneamino)phenyl]-3-hydroxyquinazolin-4(3*H*)-one (**6a**),[2] isomerised to the amide-2-[2-(4-methoxybenzoylamino)phenyl]quinazolin-4(3*H*)-one (**7a**),



6 & 7	a	b	c	d
Ar	4-$H_3COC_6H_4$	C_6H_5	4-Cl C_6H_4	4-$NO_2C_6H_4$

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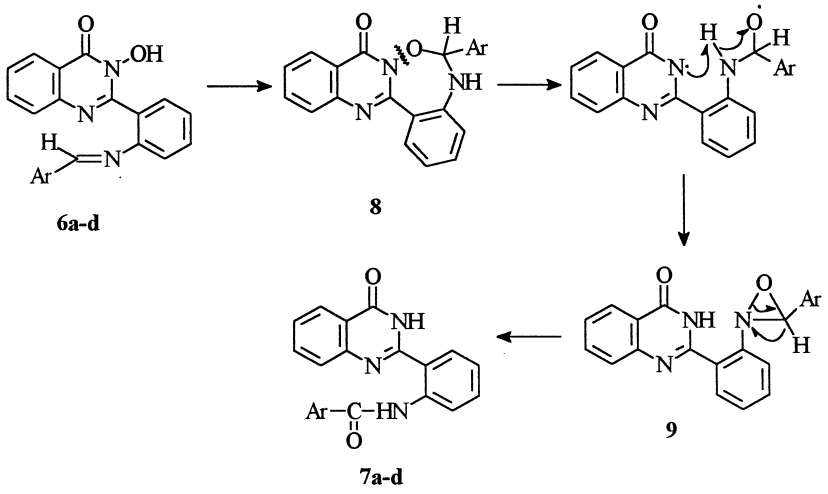
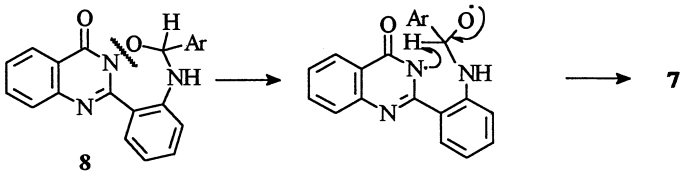
on reflux in nitrobenzene (6 h, method a), in diphenyl ether (4 h, method b) or under microwave irradiation (5 min, method c). The amide **7** was characterised by spectral data[3] and comparison with an authentic sample prepared by Butler's method.[4]

The intramolecular imine–amide conversion could be explained in two ways – (i) compound **6a** may first cyclise to an unstable [3, 1, 4]benzoxadiazepine **8**, and the labile N–O bond cleaves at elevated temperature to form an oxaziridine derivative **9** which subsequently opens to **7** (Scheme 1); (ii) the diradical formed initially by N–O bond cleavage in **8** may itself rearrange to the amide without the intervention of oxaziridine (Scheme 2).

We favour the mechanism in Scheme 1 because thermal cleavage of N–O bond in *O*-alkylated cyclic hydroxamic acids and rearrangement of oxaziridines to amides are known in literature.[5,6]



Scheme 1.



Scheme 2.

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In summary, *N*-hydroxamic acid mediating the oxygenation of an imine group can serve as a gainful reagent for >C=N- to -CONH- functional group modification.

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1. a) The mass spectrum did not record $M^{+\cdot}$ at 70 eV. The highest ion was recorded at *m/z* 222.
   b) Infrared spectrum showed carbonyl (1684 cm^{-1}) and NH (3381 cm^{-1}).
   c) ^1H NMR spectrum is characteristic by the appearance of a singlet at δ 8.4 (the methine hydrogen).
2. a) Infrared spectrum showed absorptions at 3100–2910 cm^{-1} (br, OH), 1689 (C=O) 1608 (C=N).
   b) ^1H NMR ($CDCl_3$) revealed a methoxyl group (δ 3.9, s, 3H), *para* disubstituted benzene (δ 6.9, d, $J = 11$ Hz and δ 7.65, d, $J = 11$ Hz), quinazolinone peri-proton (δ 8.35, d, 1H, $J = 10$ Hz) and azomethine proton (δ 8.95, s, 1H); Mass spectrum showed the molecular ion peak at *m/z* 371.
3. **7a**: IR (KBr): 3283, 3177, 3130, 3060, 1671 (br), 1605, 1575, 1536, 1468, 1279, 946 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.9 (s, 3H, OCH_3), 7.0–8.2 (m, 11H, Ar-H), 8.65 (d, 1H, $J = 10$ Hz, Peri Ar-H), D_2O exchangeable signals at 12.5 (s, NH) and 12.7 (s, NH). MS *m/z* 371 (M^+), 369, 353, 135, 107, 92, 77, 64.
   7b: IR (KBr): 3261, 3180, 3130, 3064, 1683 (br), 1603, 1560, 1525, 1445, 1276, 949 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.3–8.3 (m, 12H, Ar-H), 8.6 (d, 1H, $J = 10$ Hz, peri Ar-H), 12.0 (s, NH), 12.4 (s, NH); MS *m/z* 341 (M^+), 323, 294, 264, 162, 105, 77.
   7c: IR (KBr): 3271, 3128, 3060, 1685 (br), 1605, 1540, 1496, 1405, 1276, 949 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.2–8.2 (m, 11H, Ar-H), 8.5 (d, 1H, $J = 10$ Hz, peri Ar-H), 12.2 (s, NH) 12.5 (s, NH); MS *m/z* 375 (M^+), 357, 325, 135, 111, 77.
   7d: IR (KBr): 3254, 3189, 3058, 1686 (br), 1602, 1576, 1519, 1445, 1279, 947 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.25–8.25 (m, 11H, Ar-H), 8.6 (d, 1H,

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$J = 10$ Hz, peri Ar-H), 12.24 (s, NH), 12.45 (s, NH); MS m/z 386 (M^+), 368, 264, 150, 123, 119, 77.
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