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APPLICATION OF PHTHALIMIDINE SYNTHESIS WITH USE OF 1,2,3-1*H*-BENZOTRIAZOLE AND 2-MERCAPTOETHANOL AS DUAL SYNTHETIC AUXILIARIES. 2.[1] EFFECTIVE SYNTHESIS OF PHTHALIMIDINES POSSESSING BULKY GROUP AT 2-POSITION†

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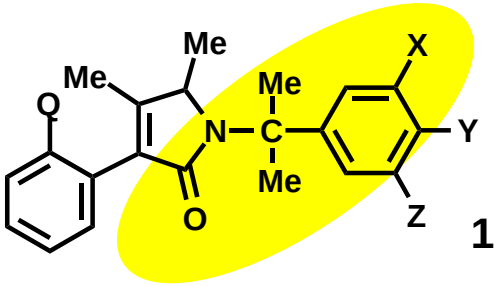
Abstract - Potentially bioactive phthalimidines are prepared in fair to good isolated yields by the 1:1 condensation reaction of *o*-phthalaldehyde with a variety of sterically-hindered primary alkyl amines in the presence of 1,2,3-1*H*-benzotriazole and 2-mercaptoethanol as dual synthetic auxiliaries.

Heterocyclic compounds containing phthalimidine (2,3-dihydroisoindol-1-one) skeletons have attracted considerable synthetic interest in recent years, because a number of fascinating natural/artificial bioactive compounds such as staurosporine (protein kinase C inhibitor), indoprofen (antiinflammatory agent) , and DN-2327 (also known as pazinaclone; anxiolytic agent) have been found to have clinical utilities.[2]



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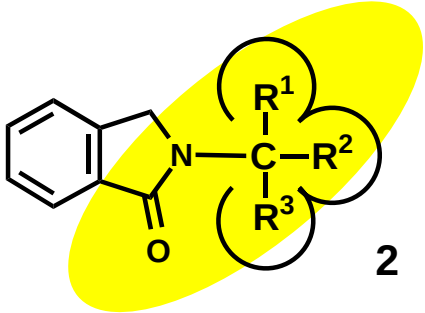


2

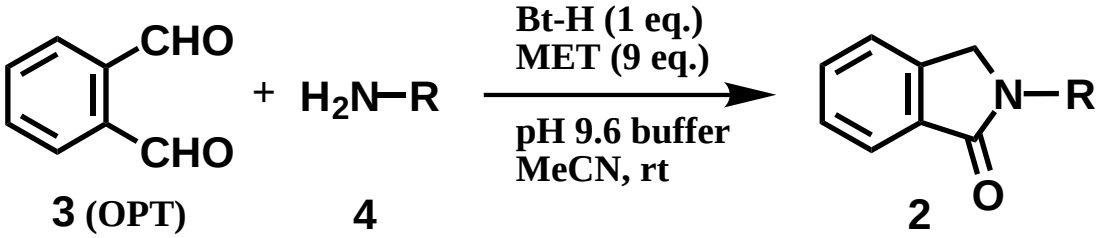
X, Y, Z, Q = H, F, Cl, Br, OMe

†Dedicated to Professor Shô Itô on his 77th birthday.

Synthetic 1-substituted 3-phenylpyrrolidinones (**1**), which have recently been used as herbicides in Chinese soils, can be characterized by sterically-hindered alkyl group at 2-position.[3] Since the structure of phthalimidine is deduced as benzopyrrolidinone, phthalimidine counterpart (**2**) of these pyrrolidinone herbicides attract our attention as clues to highly bioactive skeletons.

In general, past phthalimidine syntheses have largely depended on the Clemmensen-type reduction of corresponding phthalimide, where 2-*tert*-butylphthalimidine[4] was the only example known in literature to date; it is anticipated that severe acidic conditions may not be tolerant to tertiary alkyl groups. On the other hand, present pyrrolidinone syntheses involve the aldol-type condensation to form C3-C4 linkage as key steps,[3] which are not applicable to the formation of phthalimidine skeletons.

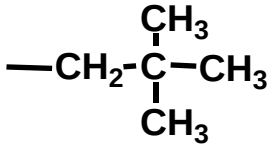
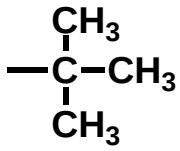
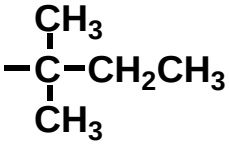
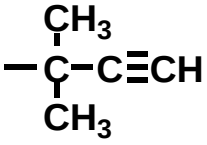
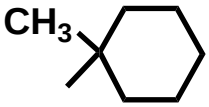
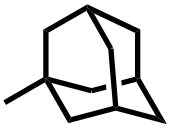
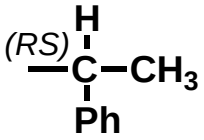
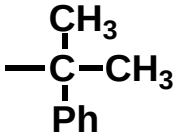
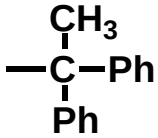
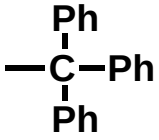
In this communication, we describe the effective preparation of phthalimidine derivatives having sterically-hindered alkyl group at 2-position, applying the recently unveiled mild-condition method based on the double Mannich reaction mediated by weak protonic acids as synthetic auxiliary.[1,5]



Sterically-hindered primary alkyl amines are either availed commercially or prepared by means of the Ritter reaction[6] from corresponding alcohols. The standard experimental procedure is as follows. To a solution of *o*-phthalaldehyde (**3**; OPT; 5 mmol) and 2-mercaptoethanol (MET; 43 mmol) in MeCN (15 mL) are added successively a solution of primary amine (**4**; 5 mmol) in MeCN (5 mL), 1,2,3-1*H*-benzotriazole (Bt-H; 5 mmol), and pH 9.6 buffer (0.05 M H_3BO_3-KCl-NaOH, 3 mL) for over 1 min each. The mixture is stirred at room temperature for 13 h. In the case where an intermediate precipitate is formed in course of reaction, the reaction time is prolonged until the reaction mixture becomes a clear solution and no starting material (**3**) is detected. After evaporation of solvent, the residue is dissolved in $CHCl_3$ (30 mL), then the organic layer is washed successively with 2 M HCl and satd. aq. $NaHCO_3$, and then dried over Na_2SO_4. Filtration followed by evaporation of solvent gives a crude product, which is subjected to column chromatography (silica gel) for purification. Results are summarized in Table 1.

Aqueous washings during work-ups are indispensable if crude phthalimidine is "reluctant" to solidify, which may reduce isolated yields when hydrophobic group is relatively small (Runs 2 and 5). When tritylamine is used as the primary amine, the yield is lowered by an unexpected formation of ditritylamine (Run 10). Otherwise, the isolated yields of 2-

Table 1. Results Using Sterically-Hindered Primary Amines.

Run	R	Time/h	Yield/%	Mp/°C
1		16	76	72-75
2		13	53	60[a]
3		13	74	120-125
4		13	68	150-154
5		13	50	oil
6		20	80	219-220
7		13	68	107-111
8		13	65	semisolid
9		13	59	semisolid
10		16	30	amorphous[b]

(a) 53.5-54 °C (ref. 4). (b) Ditritylamine (49%) is also formed.

substituted phthalimidines (**2**) are close to those in which aniline or simple aliphatic amine is used, as we reported previously.[1,5]

Preliminary bioassays of thus obtained phthalimidines show that 2-trityl derivative exhibits quite strong inhibitions on the *in vitro* grouth of L1210 and KB cells, with IC_{50} values of <4.0 and 6.3 mg/mL, respectively. These values are comparable to those by 6-mercaptopurine (6-MP; IC_{50} = 2.6 and 11.0 mg/mL, respectively), encouraging further intensive studies.

Unexpectedly, treatments of crude phthalimidines (from Runs 5, 8, 9, 10) with 25% ammonia "kick out" bulky substituents, giving 2-unsubstituted phthalimidines in *ca*. 50% yields. In addition, the treatment of 2-tritylphthalimidine with tritylamine under standard phthalimidine-forming reaction conditions[1,5] forms ditritylamine in *ca*. 50% yield. These features may represent the "tethered ion pair" of tertiary alkyl cation with a phthalimidin-2-ide anion in polar solvent systems, as has often been reported for Schiff base-benzotriazole adducts by Katritzky and coworkers.[7] Further exploitation on this class of compounds must be sought from this point of view, too.

In summary, our phthalimidine synthesis is tolerated by bulky alkyl amines, and allows the obtention of promising bioactive phthalimidines in fair to good isolated yields. Further exploitation along this line is now underway.

ACKNOWLEDGMENT

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